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TECHNIQUES FOR THE STUDY OF BEHAVIORAL EFFECTS OF DRUGS

BY

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Conference Co-Chairmen
PETER B. DEWS AND B. F. SKINNER

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* This series of papers is the result of a conference on *Techniques for the Study of Behavioral Effects of Drugs* held by the Section of Biology and the Section of Psychology of The New York Academy of Sciences, May 4, 1956.

EFFECTS OF DRUGS ON THE BEHAVIORAL PATTERNS OF CATS*

By Stata Norton and E. J. de Beer
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Many quantitative studies have been made on conditioned responses in many different species of animals. Attempts to quantitate spontaneous behavior patterns have been less numerous.

The study of behavioral patterns of animals without any experimental conditioning includes observation of the effects of inherent or genetic behavioral patterns as well as the effect of conditioning by present and past environment. The importance of inherited behavior is large in the total behavior of an animal, and some recent studies indicate that there is genetic control of very specific behavioral patterns.[5] It must be considered that the effects of drugs on spontaneous behavioral patterns, which include both environmental and genetic factors, may differ from the modifications of conditioned behavior produced by the same drugs.

A study of animal behavior without experimental conditioning can be done fairly rapidly on large numbers of animals. One requisite for such a study is that the animals must possess fairly stable personalities for reasonable periods of time under laboratory conditions, and that they must also exhibit a sufficient range of spontaneous behavioral patterns to allow studies to be made. Cats seemed to fit these qualifications and were chosen to be studied first. Other animals, such as dogs, rats, and monkeys, could also be used.

Methods

Short-haired domestic cats of both sexes were used in these experiments. The animals were all young adults. They were housed, 1 to a cage, in cages 22 inches square and 18 inches high. All cats were kept in the cages for 2 weeks before the studies were started. The animals apparently adapted well to their cages. They were fed milk and canned cat and dog food. All animals were handled several times a week even if no drugs were given.

The behavior of a large number of untreated cats was observed to find patterns that could be studied under laboratory conditions. The types of drugs that were to be studied were also kept in mind. Four broad categories of behavior were finally selected. These were: (1) Sociability, (2) Contentment, (3) Excitement, and (4) Hostility. In a general way, categories Nos. 1 and 4 were selected to represent opposite reactions of the animals directed toward the observer, and categories Nos. 2 and 3 were selected to represent opposite patterns reflecting the emotional attitude of the cat in his accustomed surroundings.

For each of these 4 general categories, 5 behavior components were chosen as convenient for study. These components were selected as a group on the basis of their tendency to occur as patterns in the control animals. For example, it was found that hissing was associated with flattening of the ears

* A preliminary report of this work has appeared elsewhere.[4]

TABLE 1
BEHAVIOR OF CONTROL CATS

Cat No.	Sociability					Contentment					Excitement					Hostility				
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
1	o	o	o	o	o	o	o	o	x	x	o	o	o	o	x	o	o	o	o	x
2	o	x	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	x	x
3	o	o	o	o	o	o	o	o	o	o	o	o	o	o	x	o	x	x	x	x
4	o	x	o	o	x	o	o	o	x	o	o	o	o	o	o	o	o	x	x	x
5	o	o	o	x	x	o	o	o	x	x	o	o	o	o	o	o	o	o	o	o
6	o	o	o	x	x	x	o	o	x	x	o	o	o	o	o	o	o	o	o	o
7	o	x	o	x	x	x	o	x	x	x	x	o	o	o	o	o	o	o	o	o
8	x	x	x	x	x	o	o	x	x	x	o	o	o	o	o	o	o	o	o	x
9	x	o	x	x	o	o	o	o	x	x	o	o	o	o	o	o	o	x	x	x
10	o	o	o	x	o	o	x	x	x	x	o	o	o	o	o	o	o	o	o	o
11	o	o	x	x	x	o	o	o	x	x	o	o	o	o	o	o	o	o	o	o
12	o	o	o	o	x	o	o	x	o	x	o	o	o	o	o	o	o	x	x	x
13	o	o	o	o	o	o	o	o	o	o	x	o	o	o	x	o	x	x	x	x
14	o	x	x	x	x	o	x	x	x	x	o	o	o	o	o	o	o	o	o	o
15	o	x	x	x	x	x	o	x	x	o	o	o	o	o	x	o	o	o	o	x
16	o	o	x	x	x	o	o	x	x	o	o	o	o	o	x	o	o	o	o	x
17	o	o	x	x	x	o	o	o	o	x	o	o	o	o	o	o	o	o	o	x
18	o	x	x	o	o	o	o	x	x	x	o	o	o	o	o	o	o	o	x	x
19	o	o	o	o	o	o	o	o	o	x	o	o	o	o	o	o	x	x	x	x
20	o	o	o	o	o	o	o	x	x	x	o	o	o	o	o	o	o	o	o	x
21	o	o	o	o	o	o	o	x	o	x	o	o	o	o	o	x	o	x	x	x
22	o	o	o	o	o	o	o	o	o	x	o	o	o	o	o	o	o	o	o	x
23	o	o	o	x	x	o	o	o	x	x	o	o	o	x	o	o	c	o	o	x
24	o	o	o	o	x	o	o	o	o	x	o	o	o	o	o	o	o	o	o	o
25	o	o	x	x	x	o	o	x	x	x	o	o	o	o	o	o	o	o	o	o
26	o	o	o	o	x	o	o	o	x	x	o	o	o	o	o	o	o	o	o	o
27	o	o	x	o	x	o	x	x	x	x	o	o	o	o	o	o	o	o	o	o
28	o	o	x	x	x	o	o	x	o	x	o	o	o	o	x	o	o	o	o	o
29	x	x	x	x	x	o	o	o	x	o	o	o	o	o	x	o	o	o	o	o
30	o	o	x	x	x	o	o	x	x	x	o	o	o	o	o	o	o	o	o	o
31	o	x	x	x	x	o	o	x	x	x	o	o	o	o	o	o	o	o	o	o
32	o	o	x	x	x	o	o	x	x	x	o	o	o	o	o	o	o	o	o	x
33	o	o	x	x	x	o	o	x	o	x	o	o	o	o	o	o	o	o	o	x
34	o	x	x	x	x	o	o	x	x	x	o	o	o	o	o	o	o	o	o	x
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38	o	o	x	x	x	o	o	o	x	x	o	o	o	o	o	o	o	o	o	x
39	o	o	x	x	o	o	o	x	x	x	o	o	o	o	o	o	o	o	o	x
40	o	o	o	o	x	o	o	o	o	o	o	o	o	o	o	o	o	o	o	x
41	o	o	o	o	o	o	o	o	o	x	o	o	o	o	x	o	o	x	x	x
42	o	o	x	x	x	o	o	x	x	x	o	o	o	o	o	o	o	o	o	x
43	o	o	o	o	o	o	o	o	o	x	o	o	o	o	o	o	o	x	x	x
44	o	o	o	o	x	o	o	o	o	x	o	o	o	o	o	o	o	o	x	x
45	o	o	o	o	x	o	o	x	o	x	o	o	o	o	o	o	o	o	o	o
46	o	x	x	x	x	o	o	o	x	x	o	o	o	o	o	o	o	o	o	x
47	o	o	x	x	x	o	o	x	x	x	o	o	o	o	o	o	o	o	o	x
48	o	o	o	o	x	o	o	x	x	x	o	o	o	o	o	o	o	o	o	x
49	o	o	x	x	x	o	o	x	x	x	o	o	o	o	o	o	o	o	o	x
50	o	o	o	o	o	o	o	o	o	x	o	o	o	o	o	o	x	x	x	x

TABLE 1. CONTINUED

Cat No.	Sociability					Contentment					Excitement					Hostility				
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
51	o	o	o	o	o	o	o	o	o	x	o	o	o	o	o	o	o	x	x	o
52	o	o	x	x	x	o	o	x	x	o	o	o	o	o	x	o	o	o	o	x
53	o	x	x	x	x	o	o	x	x	o	o	o	o	o	x	o	o	o	o	x
54	o	o	x	x	x	o	o	x	x	o	o	o	o	o	x	o	o	o	o	x
55	o	o	o	o	o	o	o	o	o	x	o	o	o	o	o	o	o	x	x	x
56	o	o	o	o	o	o	o	o	o	x	o	o	o	o	o	o	o	x	x	x
57	o	o	o	o	o	o	o	o	o	x	o	o	o	o	o	o	o	o	x	x
58	o	o	x	x	x	o	o	o	o	o	o	o	o	o	x	o	o	o	o	o
59	o	o	o	o	x	o	o	o	o	x	x	o	o	x	o	o	o	x	x	x
60	o	o	o	o	o	o	o	o	o	x	o	o	o	o	o	o	o	x	o	x
Totals.....	3	12	28	31	39	2	3	28	33	48	1	0	0	2	12	1	4	16	19	43

Symbols: x = component was present; o = component was absent.

and with withdrawing, and these reactions were therefore part of the same behavioral pattern. Likewise, purring and rubbing were associated with each other, but not with hissing.

In TABLE 1, the occurrence of the behavioral components in a control population of 60 cats is given. These data from the control cats were used to determine where significant associations existed between the components of behavior. The combined expected probabilities and frequencies were calculated for each possible pair of components. The expected frequency thus obtained was then compared with the observed frequency and the probability that the difference was due to chance was obtained by using the Chi Square Test. Pairs of components showing greater than chance association ($P = <0.45$) are shown in FIGURE 1. As this figure shows, the association within patterns was quite good.

Components Listed in TABLE 1 and FIGURE 1

Sociability. Recognition of and friendly response to the observer:

(1) Jumps up. The cat climbs, jumps, or attempts to climb or jump on the observer.

(2) Mewing. Conversational sound expressing recognition of the observer's presence.

(3) Tail up. As observer approaches or touches cat, the cat stands up with tail erect.

(4) Comes forward. As observer approaches and opens cage, cat comes forward.

(5) Alert. Cat visually follows hand or pencil moved up and down in front of it and ears are pricked forward in response to sight or sound of pencil moved along floor in front of it.

Contentment. Expression of pleasure in general surroundings:

(6) Washing. Licking fur.

(7) Kneading. Rhythmic up-and-down movements of front paws, with sheathing and unsheathing of claws.

(8) Purring. Self-explanatory.

(9) Rubbing. Pressing head and neck against cage, against observer's hands, and so on.

(10) Resting. Sitting or lying on side.

Excitement. Increased activity denoting anxious or disturbed behavior:

(11) Yowling. Harsh, loud, prolonged cries.

(12) Lashing tail. Rapid sideways movement of the tail.

(13) Piloerection. Hair erect on tail.

(14) Dilated pupil. Self-explanatory.

(15) Walking. Hyperactivity and pacing. Cat's attention not directed toward the observer.

Hostility. Expression of fear and defensive behavior. Aggressive behavior, such as clawing, biting, and advancing toward an object, appears to be a separate pattern:

(16) Growling. Self-explanatory.

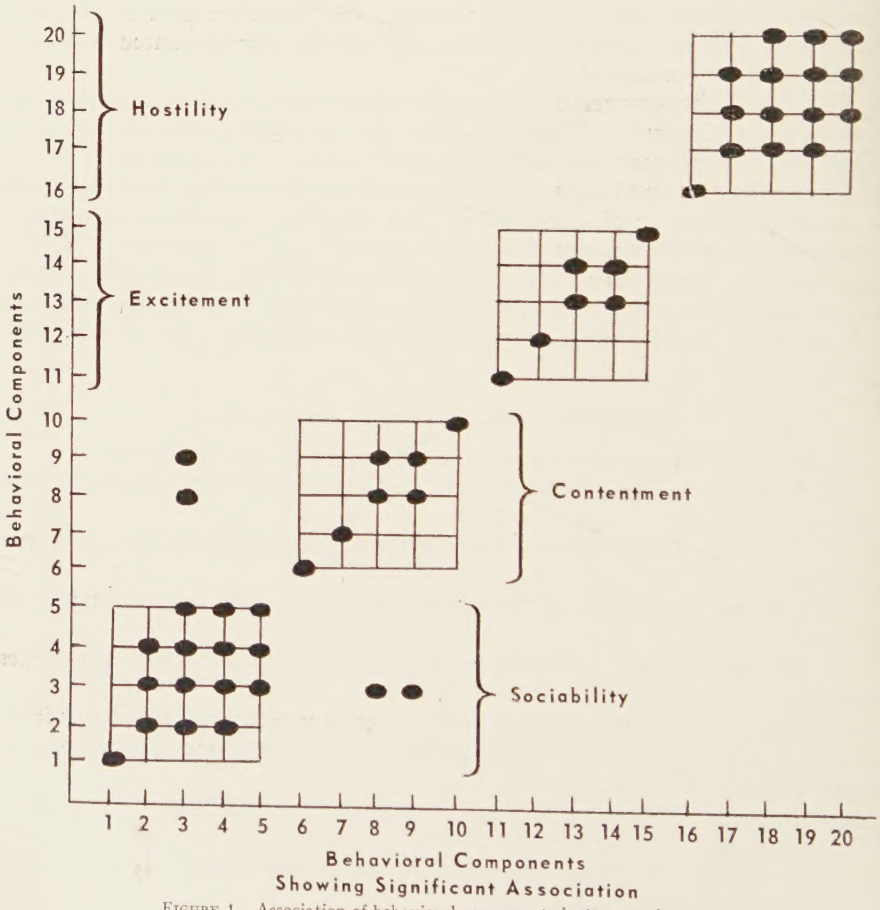

FIGURE 1. Association of behavioral components in 60 control cats.

(17) Hissing. Self-explanatory.

(18) Flattened ears. Self-explanatory.

(19) Withdrawing. Cat moves head or body away from the observer or the observer's hand when the cage is opened.

(20) Crouched. Cat sits with all 4 feet drawn under body and does not get up when touched.

In order to achieve quantitative comparisons of drug actions, these behavioral components were weighted according to the frequency of occurrence in a pattern. The component that appeared least frequently was considered to give the most information concerning the attitude of the cat, and it was therefore given the greatest number. The numbers for the individual components of each pattern were 9, 7, 5, 3, and 1 in order of increasing frequency of occurrence of the component. These numbers were arbitrarily chosen to add up to a total of 25 for each behavior pattern. In actual testing for drug effects, each cat was scored at 4 different times, and thus the maximum score for each cat for each behavior pattern was 100.

All drugs were administered orally in capsule or tablet form. For dosing, each cat was restrained in a box from which its head protruded. The cat's jaws were gently spread by pressure of the fingers, and the capsule was inserted well back on the tongue with a curved hemostat. Swallowing of the capsule was usually immediate. There was no coughing or struggling, and the cats did not appear to be disturbed by the procedure.

Two control observations were made the day before administration of the drug, and 2 more control observations were made on the second or third day after the drugs were given. No cat received drugs more than once a week, and no dose of any compound was scored unless the cat was conscious at all times after receiving the drug.

Both control behavior and behavior after drugs were observed at the same times of day. This was necessary since the cats were somewhat more restless in the morning, before feeding, than in the afternoon. The times chosen for observation were 11:00 A.M., 12:00 noon, 2:00 P.M., and 4:00 P.M. Drugs were administered at 10:30 A.M.

Results

The control behavior of some cats was found to be very stable over periods of several months, while other cats showed progressive shifts in behavior over the same period. Usually the change consisted of a gradual increase in Sociability and a corresponding decrease in Hostility. Cats that were very friendly or very hostile at the start of the experiment showed less tendency to change than cats showing a mixture of the 2 behavioral patterns. Examples of this are shown in FIGURE 2.

Six compounds and a placebo (dextrose) were tested for their effects on the behavior of the cats. The compounds were given to the cats in random sequence. Control readings and observations after administration of drugs were obtained as described above under the heading *Methods*.

The doses were as follows: dextrose, 20 mg./kg.; chlorpromazine, 15 mg./kg.; *Rauwolfia*, 50 mg. total to cats weighing less than 2 kg., and 100 mg. total to

Modification of control behavior with time							
Date	2/8	2/24	3/1	3/7	3/21	4/11	4/18
Cat No. 13							
Sociability	17	31	29	31	21	56	60
Contentment	26	35	42	40	36	31	38
Excitement	3	0	0	0	3	3	9
Hostility	11	1	3	0	0	0	0
Cat No. 15							
Sociability	3	1	0	0	0	0	0
Contentment	1	0	0	3	1	2	4
Excitement	6	3	6	20	12	19	12
Hostility	64	42	57	61	48	64	64

FIGURE 2. Modification of control behavior of 2 cats over a period of testing.

cats weighing more than 2 kg.; sodium pentobarbital, 15 mg./kg.; morphine sulfate, 20 mg./kg.; meprobamate, 100 mg./kg.; and azacyclonol, 100 mg./kg.

The scores obtained before and after treatment of each cat are given in TABLE 2.

Discussion

The frequency of occurrence of a component in a behavioral pattern may vary from animal to animal but, inherently, each animal should be able to express this action. Either through genetic or environmental control this action is not expressed. Drugs can serve as the stimulus to produce an effect (behavioral component) or to block any inhibitions preventing the response to the stimulus. In the latter case, the desired drug effect may be present, but will not be recognized if the stimulus is lacking.

If the components are incorrectly selected for a behavioral pattern, it will be impossible to demonstrate drug action. The basis for selection is the correlation of the occurrence of 1 component with others in the same behavioral pattern and the failure to correlate with other patterns.

The components are weighted according to the information contained in

TABLE 2

EFFECT OF DRUGS ON CAT BEHAVIOR

	Control Scores									Scores after Drug								
Cat No.	5	6	7	8	13	17	15	16	Av.	5	6	7	8	13	17	15	16	Av.
Dextrose																		
Behavioral pattern:																		
Sociability	57	1	21	4	17	96	1	43	30	57	0	27	13	4	89	1	50	30
Contentment	34	3	30	10	26	36	0	38	22	34	3	26	10	36	35	1	24	21
Excitement	1	1	1	0	3	0	3	0	1	2	1	0	0	0	1	3	0	1
Hostility	4	28	0	1	11	0	42	0	11	4	28	1	0	0	0	46	0	10
Chlorpromazine																		
Sociability	64	0	42	3	31	70	3	47	33	54	10	37	24	22	71	3	29	31
Contentment	32	4	48	11	35	43	1	27	25	40	4	26	12	50	34	4	35	26
Excitement	4	0	2	1	0	0	6	0	2	6	4	11	0	12	16	12	9	9
Hostility	4	33	3	3	1	0	64	1	14	4	3	4	1	0	1	21	0	4
Rauwolfia																		
Sociability	64	0	35	4	29	4*	0	44	23	49	0	8	4	14	17*	0	29	15
Contentment	40	4	35	20	42	4	3	18	21	32	4	34	9	26	12	0	24	18
Excitement	2	0	1	0	0	0	20	0	3	1	12	1	0	0	0	20	0	4
Hostility	3	36	2	12	3	20	61	1	17	4	36	2	15	0	13	64	1	17
Pentobarbital																		
Sociability	35	0	51	4	31	97	0	27	31	18	0	19	2	21	30	1	1	12
Contentment	34	4	33	12	40	36	0	17	22	20	3	9	7	23	27	4	6	12
Excitement	1	3	3	0	0	0	6	0	2	0	4	19	0	3	12	22	0	8
Hostility	4	33	4	6	0	0	57	1	13	4	8	1	9	3	0	23	1	6
Morphine																		
Sociability	50	31	36	9	21	99	0	—	35	27	16	0	0	0	0	0	—	6
Contentment	32	8	33	5	36	34	1	—	21	32	2	3	1	10	2	1	—	7
Excitement	4	2	3	1	3	1	12	—	4	24	15	52	32	15	15	20	—	25
Hostility	4	10	2	23	0	1	48	—	13	2	28	4	3	0	0	4	—	6
Meprobamate																		
	Control Scores									Scores after Drug								
Cat No.	18	20	21	22	13	17	15	23	Av.	18	20	21	22	13	17	15	23	Av.
Sociability	34	42	0	12	56	100	0	53	37	17	39	0	14	54	42	2	36	26
Contentment	26	29	4	10	31	36	2	20	20	21	26	4	10	31	23	4	34	19
Excitement	3	0	12	0	3	0	19	0	5	0	14	9	0	0	0	9	7	5
Hostility	3	0	51	12	0	0	64	0	16	0	0	37	0	0	0	42	0	10
Azacyclonol																		
Sociability	50	25	0	8	60	13†	0	—	22	22	19	0	13	22	28†	0	—	15
Contentment	43	7	3	7	38	4	4	—	15	27	4	4	13	30	4	4	—	12
Excitement	0	0	12	0	9	0	12	—	5	12	12	12	3	9	1	12	—	9
Hostility	0	3	58	9	0	0	64	—	19	0	0	64	0	0	0	64	—	18

* *Rauwolfia* administered to cat No. 14 instead of to cat No. 17.

† Azacyclonol administered to cat No. 19 instead of to cat No. 17.

each component. It is assumed that the least frequent component is the most difficult to attain, and it therefore contains the most information about the state of the cat. Thus some components are very easily evoked. Many diverse and mild stimuli, for example, can cause marked pupil dilation. This response, consequently, is considered to impart less information about the cat than the occurrence of a less frequent component, such as lashing of the tail. As another example, growling is a less frequent and a more informative symptom of hostile behavior than are flattened ears.

These 20 behavioral components of 4 behavioral patterns have been selected from many acts of cats. As more control data are obtained, it may be possible to expand or improve the classifications. Some activities of the cats were not included in the classifications because the animals were found to be too open to unconscious influence by the observer. For that same reason the scoring was done on an all-or-none basis rather than by recording the intensity of the component. Where drugs with very diverse actions are being studied, an objective test is very desirable.

Effects of Different Drugs

Dextrose. Dextrose was selected as a placebo, and no effects were expected from small amounts of this compound. As TABLE 2 shows, the 4 behavioral patterns were unaffected by dextrose.

Chlorpromazine. All the drugs reduced Sociability to some extent. Chlorpromazine caused the least reduction in Sociability and the greatest reduction in Hostility. An increase in Excitement was obtained.

Rauwolfia. Rauwolfia caused a drop in Sociability and a slight drop in Contentment, with no change in the other patterns.

Pentobarbital and morphine. Pentobarbital and morphine produced similar changes in the patterns. The most marked difference was the much greater increase in Excitement with morphine.

Meprobamate. Meprobamate, like chlorpromazine, decreased the score for Hostility, but Sociability was also decreased. This can hardly be ascribed to sedation or anesthetic effects, because neither the Contentment nor the Excitement patterns were changed.

Azacyclonol. Azacyclonol resembled *Rauwolfia* in its effects on the 4 behavioral patterns. The principal action of this drug was again to decrease the Sociability score. Hostility was unchanged, and Excitement increased slightly.

The correlation between changes in cat-behavior patterns and the effects of drugs on the human psyche remains to be established. It is true that positive changes in each case were obtained with these drugs, all of which are reputed to affect human mental processes. It is also true that dextrose had no effect, and that none was expected.

Masserman[3] and Jacobsen and Skaarup[1,2] have investigated the effects of drugs on induced conflict behavior in cats. Masserman found that alcohol abolished neurotic behavior in cats to a certain degree. Jacobsen and Skaarup, however, did not find that chlorpromazine produced any reduction of conflict behavior.

The work described in the present paper does indicate that, so far, drugs

having effects on the psyche produce changes in spontaneous behavior. Further work will be needed to determine whether each drug produces characteristic changes in pattern or whether these changes will be similar for similar types of pharmacological effects. It is hoped that the techniques outlined in this paper eventually will provide a means of estimating the relative potencies of the drugs discussed here as well as classifying them qualitatively.

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SOME EFFECTS OF DRUGS ON CLASSICAL (TYPE S) CONDITIONING*

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Part of the program at the University of Chicago psychological laboratory has been a rather extensive series of experiments on conditioned fear (or "anxiety") in rats. At the time we initiated this enterprise we elected to follow a general method differing somewhat from that commonly employed in experiments in this area of investigation. Customarily, workers had been using instrumental avoidance or escape responses as indicators. Our interest in emotional conditioning included substantial curiosity about the effects of several variables, such as electroconvulsive shock, cerebral ablations, and drugs, that might influence mobility or produce psychic or somatic debilitation. The usual avoidance, escape, or maze paradigms do not allow for an evaluation of the specific effects of such variables on the conditioning of animals, independently of the general effects of these variables on motility and general well-being. An alternative approach that would supplement and crosscheck the findings of other investigators seemed worth pursuing. Furthermore, avoidance and escape behavior can become quite complex theoretically. We hoped to avoid distraction in useless academic controversy by emphasizing a most elementary paradigm amenable to experimental and logical analysis within the framework of the most empirical sort of descriptive behaviorism.

Instead of studying an instrumental avoidance response that many would consider to be mediated by and dependent upon a conditioned fear response that has drive properties, we have attacked the conditioned fear response directly, and we use what appears to be an unlearned reflex pattern of response as the indicator. The general outlines of the method resemble the Watson and Raynor[17] efforts vis à vis little Albert. Most of our experiments, more specifically, have followed the Estes and Skinner model,[4, 9] in which a conditioned emotional disturbance superimposed upon a lever-pressing habit interferes with the emission of lever responses. In our major experiments, after a stable lever-pressing habit for variable-interval reinforcement has been established, the animal receives a series of emotional-conditioning trials during lever-pressing runs. Each trial consists of a 3-minute presentation of a conditioned stimulus (CS), usually a clicking noise or a blinking light, terminated approximately contiguously with 2 momentary electric shocks to the feet (each from 0.6 to 1.5 mAmp. intensity for approximately 0.2 seconds). After a few such pairings, the CS acquires the power to reduce the rate of lever pressing, or to stop it completely. Usually the animals also defecate during the run. This change in rate of lever pressing we have called a conditioned emotional re-

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sponse (CER), "conditioned" in that a neutral stimulus acquires the power to evoke it, "emotional" in that it includes defecation as part of the pattern and in that its development depends upon painful stimulation, and "response" in that it consists of an objectively identifiable change in behavior. We did not originate the technique, we only took advantage of it. Other investigators, quite independently of us, have seen the utility of this approach and have developed similar methods.

The superimposition of conditioned fear on some regularly recurring behavior such as lever pressing permits a distinction between the loss of conditioned fear behavior as a function of general deterioration and its loss as a function of more specific action of the experimental variable on some aspect of the conditioning as such. Furthermore, as the operant here used can be varied in strength by manipulation of the parameters that control it, this arrangement allows us to adjust the sensitivity of the tests and permits some reasonable beginning at quantification of the strength of the fear response. Furthermore, the interactions between the CER and the lever pressing provide some leads as to the ways in which "emotional" and "nonemotional" behavior may modify or be organized with respect to each other. Discussions of these topics and of the effects of variables such as convulsions and certain cerebral ablations need not concern us here.[1, 3, 9, 10, 12, 13]

For the present discussion, I should make clear that our interest with respect to drugs has emphasized the selective use of pharmacological agents and other procedures to increase our understanding of the CER, rather than the use of the CER to study drugs. To a former clinician, behavior of this class is of the most central interest. A substantial fraction of the behavior usually considered under such headings as personality, psychopathology, values, attitudes, and the like, probably depends in one way or another upon learning akin to that which CER conditioning produces.

Almost from the beginning, it has been clear that the CER is both acquired and lost in accordance with the laws of Type S conditioning and extinction.[15, 16] Observation of the animals in the boxes during elicitation of the CER revealed the animals to be engaged in crouching or "freezing," and usually defecating, as rats so commonly do in the early stages of traditional avoidance conditioning. This pattern cuts across or replaces lever pressing, and it does not appear to be an artifact arising out of accidental punishment of a lever response or other interaction with that behavior. A CER established in the box can be elicited by presentation of the CS in a grill box (a chamber with a grill floor but no lever) without any additional training or adaptation. Similarly, a CER established in the grill box can be elicited in its standard form even though no lever pressing has ever occurred there, and it can be transferred directly to the lever-pressing situation without further training if the original conditioning is strong enough. Except under a few unusual circumstances, the overt expression of the CER, when established in accordance with the fundamental Type S paradigm of CS for several minutes terminated with the unconditioned stimulus (UCS), is uniform and predictable. Nor can the CER be altered by shocking the animal when it begins to crouch. Such punishment

only increases the intensity of the overt response and the power of the CS to evoke it.[8]

We consider the overt CER (crouching and defecation) as an unlearned reflexive expression or side effect of emotional disturbance, much like the psychogalvanic response in man. Also, the overt CER seems to be a clear instance of "respondent" behavior. The overt response appears when the animal is afraid, and the Type S conditioning procedure makes it afraid of the CS. With this analysis, the overt CER turns out to have some of the same weaknesses as an indicator as does ordinary instrumental avoidance behavior, except that the CER indicator is "wired" into the animal and does not have to be learned instrumentally.

One of our early papers[10] presented data indicating that the CER may be amenable to "nonresponse extinction." Earlier, in his doctoral research, Brady[2] had found that a CER, attentuated by electroconvulsive shock (ECS), reappeared at one time or another within the first 30 days after the last convulsions. We wondered what its status was during the posttreatment interval in which it was not perceptible in the animal. We found that unreinforced presentations of the CS, to animals that no longer showed the CER in the grill box after ECS, prevented the normal return of this conditioned response 2 weeks after the last "extinction" trial and a little more than 30 days after the last convulsion. Here we had a Type S extinction operation on the CS in the absence of the overt but unreinforced occurrence of the conditioned response that influenced the subsequent strength of that response. We did not consider this to be a test of any current behavioral theory, because more sensitive measurements in the lever box (experiment 2) revealed to the practiced eye that a greatly truncated or attenuated form of the CER probably was occurring in many animals during early extinction trials. Whether we had nonresponse extinction or not depended upon the definition of the response. While we could have performed the obvious technical *tour de force* of repeating the experiment with more ECS so that no discernible expression of the CER appeared even in the lever box during the extinction process, such a procedure appeared rather nonproductive except for purposes of controversy. The issues never would have been clear. For example, the critic could maintain that the continued water reinforcement for lever pressing during the post-ECS extinction trials might strenghthen the lever response so much that the CER would not have a fair chance to appear on the final test trials.

As one aspect of our subsequent program, we began a series of rather informal exploratory experiments on CER conditioning in the grill box, testing the effects of various intercurrent medications and other procedures on the acquisition and extinction of the CER. Perhaps the most intriguing of these experiments has been the experiment by Peter Jernberg and myself[11] on the effect of intercurrent medication with chlorpromazine on the conditioning and extinction of the CER.

A preliminary, informal report by Altschule, Bower, and Cook* indicated that chlorpromazine "blocked" a conditioned avoidance response in the rat,

* Described in a mimeographed summary of research on chlorpromazine circulated by Smith, Kline & French Laboratories, Philadelphia, Pa. The original report has not been seen by the author.

though the animals still responded to the shocks. These workers used a heavy dose (10 mg. kg. administered subcutaneously), and found the maximum effect $2\frac{1}{4}$ hours after injection. In their experiment, the rats learned to avoid an electric shock to the feet by jumping up on a suspended pole. A bell was rung just as the shocks were to be presented. The rat could therefore avoid the shock by jumping when it heard the bell.

In preliminary experimentation, we had found that doses of chlorpromazine as low as 1 or 2 mg. kg. administered subcutaneously interfered with learned behaviors such as lever pressing, and it also tended to interfere with the elaboration of the typical freezing and defecation resulting from the CER in animals already conditioned. From this, it appeared possible that the loss of a conditioned avoidance response, as in the Altschule, Bower, and Cook study, could be attributed either to some effect of the drug on operant behavior in general or to a more specific blocking of the conditioned fear upon which instrumental avoidance behavior is commonly thought to depend. The present experiment was intended to help clarify this ambiguity by studying the effects of chlorpromazine on the CER more intensively and directly.

Part 1 of the experiment checked the effects of chlorpromazine on the conditioning of the CER in the grill box, using 3 groups of 6 rats each, as follows:

Group 1. These animals were subjected to a total of 3 standard CER conditioning trials in the grill box, each trial consisting of a 3-minute presentation of the CS, a clicking noise, terminated contiguously with 2 momentary shocks to the feet of 1.0 mAmp. intensity. The first 2 trials were separated by 1 day of rest and 2 days of adaptation in which the animal ran in the apparatus but received no CS or UCS. The second 2 trials were separated in the same way.

Two and one quarter hours before each conditioning trial, the animals in this group received 10 mg. kg. of chlorpromazine subcutaneously. They also received chlorpromazine on 1 of the adaptation days and saline on the other, between each conditioning trial.

Finally, following 1 adaptation day, the rats were tested for retention of the CER, and the response was extinguished by daily unreinforced presentation of the CS, all under saline. These tests started from 48 to 50 hours after the last dose of the drug.

Group 2. These rats were treated exactly as those of group 1, except that they received saline injections rather than the drug during both conditioning and extinction of the CER.

Group 3. These rats were treated exactly as the animals of group 1, except that they never received any reinforcing pain shocks with the CS. This third group was included to find out whether chlorpromazine altered the native or unconditioned response to the relatively neutral CS. Also, our own preliminary observations and similar ones made independently by Gordon Heistad[6] suggested that, under the drug, animals sometimes responded to this neutral stimulus in a way reminiscent of the standard CER in the absence of any conditioning experience. We wanted to eliminate the possibility that such an incidental reaction might become conditioned to the CS, even without shocks, to confound our findings for group 1.

In part 1 of the experiment, the effect of the drug on acquisition of the CER would be expected to appear in the performance of the animals of groups 1 and 2 during the subsequent extinction trials given under saline. If chlorpromazine blocked conditioning, the rats conditioned under the drug would not show the CER when tested with an unreinforced presentation of the CS under saline.

All animals in groups 1 and 2 showed the CER when tested under saline, as indicated by freezing and immobility in response to presentation of the CS in the first extinction run. The animals in group 1, conditioned under chlorpromazine, showed weaker CER, however, as indicated by less prolonged freezing during the first extinction trial as a whole and by the lower resistance of their conditioning to experimental extinction. Further, the rats conditioned under the drug showed a somewhat lower incidence of defecation during the CER-extinction process. In general, the group 1 rats differed from the group 2 animals conditioned under saline much as the animals conditioned with low-intensity shocks (0.6 mAmp.) differ from those conditioned, as these rats were, with 1.0 mAmp. shocks.

The rats of group 3 (given the CS alone when under chlorpromazine) showed no signs of the CER or other emotional disturbance when tested under saline. They had never had the CS paired with shocks.

Though chlorpromazine in the dosage used here renders the animal ataxic and thus precludes assessment of the CER as indicated by freezing under drug conditions, some data appeared during the conditioning trials that suggest that the drug does block, in some way, the reflex (autonomic) expression of fear. Earlier research has indicated that defecation can be used, in CER conditioning, as an indicator response.[10] Here, the animals of group 1 under chlorpromazine showed a significantly lower incidence of defecation than the group 2 animals in the first and second conditioning trials [probability (P) = 0.008].[5] This difference just failed to achieve significance in the third conditioning trial because of an atypical decrease in incidence of defecation among the saline-control rats of group 2.

Part 2 of the experiment checked the effect of chlorpromazine on extinction of the CER. All rats were conditioned exactly as were those in group 2, except that no saline was injected. All of the animals had acquired a strong CER by the third conditioning trial, as indicated by crouching and immobility in response to the CS, and all but 2 defecated. They were then divided into 2 groups of 9 each and treated as follows:

Group 1. These animals received a total of 14 extinction trials similar to those given in part 1 of the experiment. For each of these trials, the rats were prepared by a dose of 10 mg. kg. of chlorpromazine, administered subcutaneously 2¼ hours before the run.

Group 2. These animals received the same extinction procedure as those in Group 1 except that they received injections of saline.

After 1 day of rest and 48 to 50 hours after the last injection, all of the rats received saline and, 2¼ hours later, a postextinction test in the grill box. Two additional extinction runs under saline were given to all animals, 1 test on each of the next 2 days. The performance of animals in group 1 during these final

tests under saline was observed in order to discover whether the extinction process under chlorpromazine had had the normal decremental effect on the CER.

On the first postextinction test, all animals of group 1 and only 2 animals in group 2 showed the typical immobility in response to the CS ($P < .005$), and 5 of the group 1 animals and none of the group 2 animals defecated ($P < .015$). The difference in incidence of crouching and immobility remained just as significant on the next 2 test-extinction days. The difference in defecation was still significant at the 0.04 level on the second day, but it had almost disappeared by the day following.

Chlorpromazine in these heavy doses does not block CER conditioning, although the drug does interfere somewhat with such conditioning. Rats conditioned under the drug with 1.0 mAmp. shocks behave during the extinction process under saline in a manner similar to that of rats conditioned in the usual way with 0.6 mAmp. shocks. The drug does appear to block experimental extinction quite decisively, however. As yet we are unwilling to venture a firm explanation for this intriguing but somewhat paradoxical finding. The findings for part 1 of the experiment indicate that rats on this dosage of chlorpromazine can hear the CS and become conditioned to it and to the apparatus, even though they are so ataxic that they cannot or do not elaborate a regular CER pattern of crouching and tense immobility. The absence of defecation among drugged but conditioned rats in part 2 of the experiment that defecate in response to the CS under normal conditions suggests that chlorpromazine may have blocked the motor or effector side of the CER in such a way that the response did not appear without reinforcement during the extinction process under the drug. From our earlier findings on "nonresponse extinction" of the CER, however, we would not necessarily expect the nonoccurrence of a full CER during extinction trials to prevent experimental extinction.

Perhaps the extinction process in part 2 of the experiment failed to take effect simply because the drugged state and the normal state must differ so much with respect to the pattern of afferent stimulation and what might be considered as the animal's "sensorium" that the extinction process could not generalize from one to the other. Certainly, from the diffuse and interesting pharmacological and physiological effects of chlorpromazine, one would expect this difference to exist. Our experience with the CER, however, indicates that both conditioning and extinction generalize quite broadly, particularly in the case of CER based on as few conditioning trials as were employed here.

When we inspect some of our data[8] produced by a comparable experiment in which amphetamine rather than chlorpromazine served as the intercurrent medication, however, we find something quite different. Here we had 1 group conditioned under amphetamine and the conditioning extinguished under saline, 1 group given the CS only under amphetamine and then under saline, 1 control group conditioned and the conditioning extinguished under saline, and 1 group conditioned under saline and the conditioning extinguished under amphetamine. The rats received either 2.5 mg./kg. of racemic amphetamine 30 minutes before the grillbox run, or equivalent saline administered subcuta-

neously. To summarize these data, amphetamine interfered only slightly with conditioning and even less, if at all, with extinction, even though the drug made the animals hyperactive, so that crouching and immobility were uncommon, and even though it blocked defecation somewhat. The interference with conditioning was approximately similar to that encountered with chlorpromazine in that the animals conditioned under amphetamine later behaved, under saline, much as did the rats given CER conditioning with 0.6 mAmp. shocks rather than the 1.0 mAmp. shocks they received. This finding is quite in keeping with the known slightly analgesic effects of the drug. Here conditioning and extinction of the CER went ahead quite satisfactorily even though the animal was under the influence of a drug that alters autonomic function and has central stimulatory effects as well. The incremental effects of reinforcement and the decremental effects of nonreinforcement under amphetamine generalize to survive the changes produced when the effect of the drug wears off.

Robert Y. Moore and I subsequently engaged in more direct investigation of the role of the sympatheticoadrenal system in CER conditioning. In 1 experiment, 8 completely adrenalectomized (ADX) and 11 sham-operated rats were compared with respect to acquisition and extinction of the CER in the grill box. The ADX animals had free access to salt water during the entire experiment, this procedure having proved more efficacious than endocrine supplement in maintaining such animal preparations. All ADX rats died within 30 days after the end of the experiment when the salt water was removed, indicating that the adrenalectomy was complete. No differences in conditioning or extinction appeared between the experimental and the control groups.

In another experiment, following the essential method described in the chlorpromazine and amphetamine experiments, Moore and I studied the effects of methantheline bromide or Banthine* on conditioning and extinction of the CER. In this case, the rats received intraperitoneally either saline placebo injections or 25 mg. kg. of Banthine 1 hour before the experimental runs. This drug acts as a ganglionic blocking agent on both the sympathetic and parasympathetic divisions of the autonomic nervous system, and it exerts a potent additive atropinelike action at the postganglionic nerve endings of the parasympathetic system. We understood that the drug does not get through the blood-brain barrier to a substantial extent because it is a quaternary amine, but that it would produce massive disruption of the normal autonomically mediated effector patterns. Again, to summarize these data, though the rats conditioned under Banthine later showed the CER when tested under saline, the drug had interfered somewhat with conditioning. The incidence of the full CER, as defined by tense crouching among rats conditioned under the drug, was significantly below the incidence among control animals ($P < .023$), and the CER differed qualitatively from that normally to be expected with 1.0 mAmp. shocks. The difference was not like that found in the earlier experiments, where the drug appeared to produce effects similar to those found with weaker shocks. On the contrary, the animals condi-

* A product of G. D. Searle & Co., Chicago, Ill.

tioned under Banthine showed very generalized responses, crouching in response to being placed in the apparatus or intermittently throughout the run, and not at all like the nicely discriminated CER we found among the rats conditioned under amphetamine. The drug similarly appeared to interfere somewhat with experimental extinction. After 10 extinction trials, only 8 of 19 rats extinguished under placebo still showed the CER while 8 of 10 rats extinguished under Banthine still retained it, a difference, however, that is not clearly significant statistically ($P > .05$).

This was a very preliminary experiment, and our choice of drug probably was inappropriate for these purposes. Banthine produces a severe intestinal stasis and, in this dosage, it appeared to make the animals ill. We had to disrupt the normal routine every 3 days and take the animals off the drug to allow them to empty their intestines. The differences between the drugged and the control rats, where clear, were of the sort we normally see in indisposed animals. This factor, rather than specific autonomic effects of the drug on critical components of the CER could account for the results. At present we are following up this problem by using an autonomic blocking agent with a drastically shorter duration of action.

Several years ago, Robert W. Goy and I checked the effect of ether anesthesia on acquisition and extinction of the CER, again following this same paradigm. Here, the control animals were conditioned and extinguished in the grill box in the usual way. For each conditioning trial those rats conditioned under ether received ether inhalations until they lost the corneal reflex, and then they were placed in the apparatus and allowed to recover. When the postanesthetic hyperactivity developed, the CS was turned on for 1 minute and terminated with 2 shocks to the feet of 1.5 mAmp. intensity. The rats squealed and jumped, of course, when the shocks were given. We found it impossible to condition the CER in the experimental animals, even after a number of conditioning trials considerably in excess of the 2 or 3 required to develop a clear CER in normal rats. Extinction trials given under identical conditions of postanesthetic hyperactivity failed to weaken a CER established under normal conditions. After all control rats had lost the CER through extinction, those animals that had received their extinction trials under ether showed the CER at full strength when tested under normal conditions. These findings were anticipated. That humans and animals under light anesthesia may show clear reflexive reactions to painful stimulation and yet show no "memory" of the event is common knowledge, but these findings interested us because we were seeking to identify some limit beyond which the animal could not be altered without disrupting the necessary conditions for acquisition of the CER.

General Comments

One cannot help but notice that much of the animal experimentation with respect to the behavioral effects of the tranquilizing drugs employs a paradigm in which the indicator behavior, instrumental or respondent, develops as a function of painful stimulation and disappears among normal animals when such stimulation is omitted. The analogy between these behaviors and

emotional-motivational disorders among humans, though seductive, may be quite misleading. I am not sure that the tranquilizing drug of choice will necessarily be one which will obtund the CER or break up instrumental avoidance behavior, nor am I sure that we should even want to use a drug that had this effect. Such a drug might well produce a sort of psychopathic irresponsibility, as can be seen in our social experiences with alcohol, or it might have other undesirable effects more serious than the ills it alleviates.

I make a special point of this because, in informal conversations with other workers, I have heard of drugs that might have potentialities written off as effective tranquilizers simply because they do not weaken an avoidance or fear-type response. In some extremely preliminary work at the University of Chicago we have encountered just such a problem. John Harvey, William Beckwith, and I[8] have some data that indicate that meprobamate (at 80, 160, and 240 mg./kg., injected intramuscularly) does not disrupt lever pressing for variable-interval water reinforcement, nor does 80 mg. kg. of meprobamate, injected intramuscularly, interfere noticeably with the acquisition, expression, or extinction of the CER in the experimental box. Observations made during the handling of the drugged rats strongly suggest that these animals are more relaxed and calm than normal trained rats usually are under the 23-hour water deprivation employed here. While these experiments were being performed, a colleague, Eckhard Hess,[7] was searching for a method to reduce the emotionality of some newly hatched ducklings, as part of his research program on "imprinting." The birds very quickly and quite indelibly became attached to the object or animal to which they were exposed under the proper conditions at a critical period shortly after hatching. While surgical intervention can influence emotionality here, insult to the nervous system has consequences in other spheres that complicate interpretation of the results. Meprobamate was suggested as a drug that might reduce emotional disturbance without markedly influencing motility or coordination. In his preliminary work with meprobamate in imprinting, Hess found that the drug completely blocked normal imprinting when given to the ducklings shortly before their experimental runs at the critical age. Further, he found that ducklings given the drug just at the beginning of the critical period could be imprinted readily 14 hours later at an age at which the birds normally do not imprint well. Meprobamate given an unimprinted duckling beyond the critical age for imprinting reduces the bird's emotional disturbance, but does not make it easier to imprint it at that time. Finally, Hess's data suggest that meprobamate does not prevent the appearance of learned avoidance behavior in 7-day-old ducklings conditioned normally, even though it seems to reduce the symptoms of generalized emotional disturbance. If Hess and I are correct in believing that imprinting, emotional disturbance, and the CER are akin, we have intriguing evidence that suggests that meprobamate may influence decisively a process that depends in some way upon emotional arousal, even though the drug does not block behavior that most of us consider to depend upon a conditioned emotional disturbance or some form of aversive conditioning.

The point to be made here is that we probably shall have to achieve new levels of sophistication before we can specify adequate screening procedures for the

tranquilizing drugs. Further analysis of the aversive case in behavior theory and a new look at the problems of fear, anxiety, and symptom formation in human psychopathology are absolutely essential. This analysis and scrutiny will be facilitated greatly if accompanied by a liberal allowance of intelligent but open-minded skepticism and plain old simian curiosity.

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MODIFICATION BY DRUGS OF PERFORMANCE ON SIMPLE SCHEDULES OF POSITIVE REINFORCEMENT*

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The basic elements of technique for the use of the free operant are by now quite well-known.[3] The purpose of this paper is to illustrate the use of the technique for drug studies by showing how 1 particular procedure has been used to start the analysis of the behavioral effects of some drugs. The work described here has been done on pigeons kept close to a constant weight of between 80 and 90 per cent of the weight at which they stabilized when fed *ad libitum*. The pigeons were trained to work as previously described, the arrangement being shown in FIGURE 1.[1, 2] They pecked at a translucent plastic disk that had variously colored lights behind it. Each peck broke a circuit that enabled it to be recorded and counted. According to a schedule, the pigeon was rewarded ("reinforced") for pecking with food from a tray that rose so that the food was accessible to the bird for 5 seconds.

The distribution of pecks in time, that is, the rate of pecking from time to time, is extremely sensitive to the precise contingencies relating pecks to rewards. For example, if every sixtieth peck is rewarded under the conditions of our experiments, the pigeon comes to peck at high sustained rates. This is a fixed ratio schedule; there is a fixed ratio of reinforcements to pecks. Henceforth this performance will be referred to as "ratio performance." On the other hand, if a single peck is rewarded when, and only when, a constant interval of time (for example, 15 minutes) has elapsed, there is a period at the beginning of the interval when the bird does not peck at all, and then there is a fairly smoothly accelerating rate of pecking until the rewarded peck. This is a fixed interval schedule; a fixed interval of time must elapse before a reward can be obtained, and the pattern of pecking engendered by it will be referred to as "interval performance." It can be arranged that when a light of one color is on, the schedule is fixed ratio, and when a light of a different color is on, the schedule is fixed interval. The bird comes to perform appropriately to each of the schedules according to which light is on. Thus the bird's performance can be observed on more than 1 schedule during a short period of time without disturbing the animal in any way. This is a "multiple schedule" in the terminology of Ferster and Skinner.

Pigeons have some advantages for this type of work.[4] They stay adult and in their prime for many years without apparent change. They very rarely show signs of disease and they stand food deprivation for long periods without obvious ill effects. Their food, grain, is very convenient both for use in an automatic magazine and for daily weighing to maintain the birds close to constant weight. Their excellent vision makes use of colored lights as discriminant stimuli possible. These lights are very convenient and make it

* This work was supported by funds received from the William F. Milton Fund of Harvard University, Cambridge, Mass., the Roche Anniversary Foundation of Hoffmann-La Roche, Inc., Nutley, N. J.; and a grant (No. M 1226) from the National Institute of Mental Health, National Institutes of Health, Public Health Service, Department of Health, Education, and Welfare, Bethesda, Md.

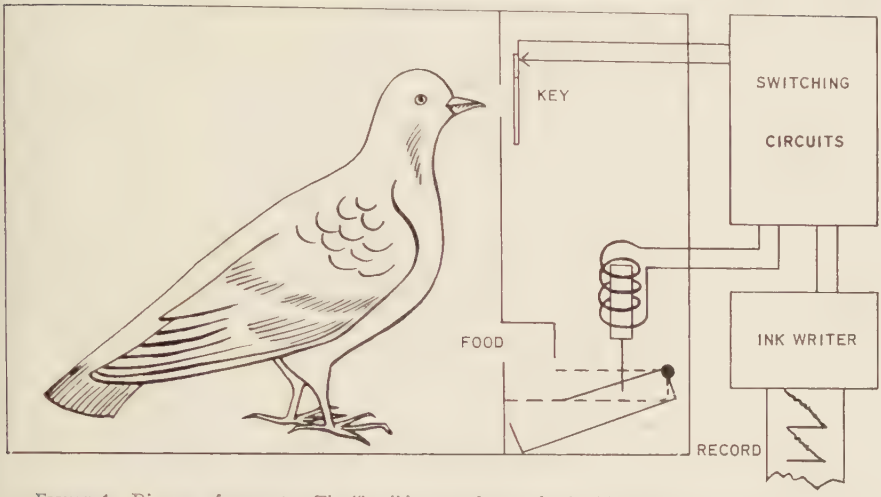

FIGURE 1. Diagram of apparatus. The "key" is a translucent plastic disk with variously colored lights (not shown) behind it. The food is normally out of reach of the pigeon, but it can be made available by the activation of a solenoid.[1] (By permission of Williams and Wilkins Co., Baltimore, Md.)

easy to employ many different stimuli in a single experiment. Perhaps the most important advantage is the relative "pureness" of the behavioral "response" used; that is, the peck. The pigeon can operate the key only with its beak, and although the precise topography of the peck undoubtedly varies from time to time, the variation is necessarily within fairly narrow limits. This is not always true for most other species and it is perhaps the main reason why, by and large, experiments on pigeons seem to progress faster than those performed with other species—a by no means unimportant consideration in a new branch of science. The main disadvantage of the use of pigeons is the great phylogenetic gap between birds and humans. All that one can say is that the general laws of operant behavior seem to show remarkable constancy from species to species, and that so far we have not found drug effects in pigeons that outrageously contradict the known effects of the same drugs in humans. On the contrary, the effects seem quite analogous.

A specific multiple schedule used extensively is illustrated in FIGURE 2. When there was a red light behind the key the bird was rewarded on the sixtieth peck made (fixed ratio), and when there was a blue light behind the key the bird was rewarded for the first peck made when 15 minutes had elapsed since the preceding reward (fixed interval). The standard "run" consisted of the following sequence: fixed ratio, fixed interval, fixed ratio, 2 fixed intervals, 10 fixed ratios, 2 fixed intervals and 3 fixed ratios. It can be seen that as soon as the red light came on, for example, as at the beginning of the series labelled "ratios" in FIGURE 2, the bird immediately started to peck at a high rate that was maintained until reinforcement. On the other hand, when the blue light came on, as at the beginning of the period labelled "interval" in FIGURE 2, the bird waited several minutes before pecking and then showed a gradual increase in rate up to reinforcement.

FIGURE 2. Record of a typical standard run on the multiple schedule used in most studies. Abscissa = time; ordinate = cumulative number of pecks. The scales are as shown. The short diagonal lines on the record show the occurrence of rewards.

When the birds were given this standard run daily, the whole performance became stable and reproducible, and it remained so indefinitely or, at least, over a period of many months.

Eight birds were given 30 mg. of phenobarbital sodium intramuscularly,*

* In all of the work described in this paper, the birds were given a constant dosage of the drug, irrespective of the weights of the different birds. This is because, in general, we were concerned with the comparison of drug effects in the same bird or birds. In fact, the birds differed so little in weight (about plus or minus five per cent of the mean weight of the birds used in this series of experiments) that the doses were almost constant in terms of dosage per kilogram. Since the mean weight of the birds was 435 gm. the dosages per kilogram are rather more than twice the dosages shown in the text and in TABLE 1.

and then put through the standard run at various times after injection. To minimize reduction in photographic reproduction, only selected parts of each run for a single bird are shown in FIGURE 3 and those following, and the parts chosen are the single interval and the 10 consecutive ratios labelled in FIGURE 2. At 3 hours after injection (Record A, FIGURE 3) interval performance was almost abolished and ratio performance much disturbed. At 24 hours, ratio performance was almost normal, while interval performance was still profoundly disturbed (Record B, FIGURE 3). The initial pause was lost and the bird pecked irregularly through the whole interval. The rate was constantly changing although the changes were quite smooth, so the cumulative record shows a succession of rounded convexities and concavities. Recovery proceeded progressively and essentially normal interval performance had returned by 50 hours (Record D, FIGURE 3).

Similar experiments were conducted following injection of 3 mg. of methamphetamine. This dose of drug did not appreciably affect ratio performance (FIGURE 4), while interval performance was greatly changed. As was the case following phenobarbital, the initial pause was lost, but the rate of pecking showed abrupt changes from high rates to zero, giving a steplike appearance to the cumulative record. This phenomenon is best seen in Record C of FIGURE 4, but can also be seen in Records B and D. As might be expected, administration of the central nervous system stimulant methamphetamine leads to an increase in the total number of pecks made (Records A and B, FIGURE 4) in contrast to the early decrease caused by the depressant phenobarbital. A final point of interest is that the pigeon ignores one of the food presentations in the ratio series (FIGURE 4). This is indicated by a discon-

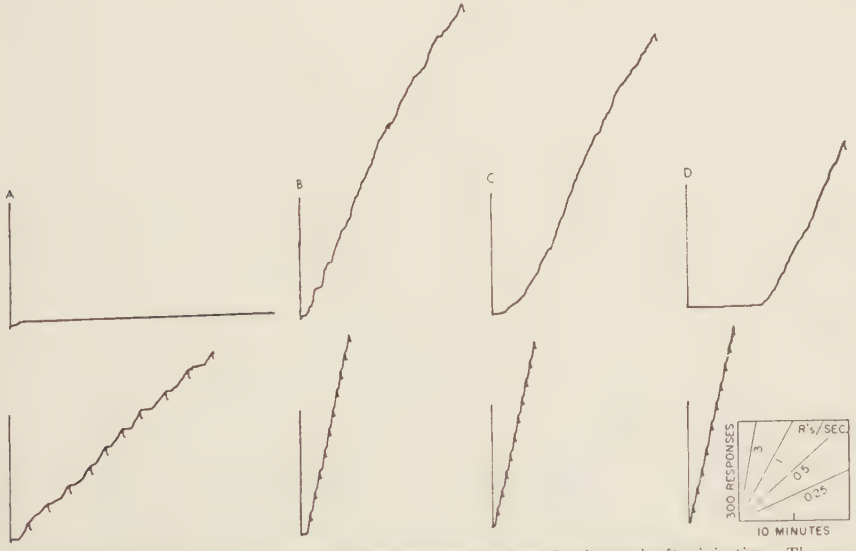

FIGURE 3. The effects of phenobarbital on performance at various time intervals after injection. The upper series shows the selected interval, and the lower series shows the 10 ratios. The interval above each sequence of ratios is from the same standard run.
Symbols: A = 18 hours, B = 24 hours, C = 36 hours, and D = 48 hours after injection.

FIGURE 4. The effects of methamphetamine. The schedule and arrangement is the same as that in FIGURE 3.
Symbols: A = 4 hours, B = 20 hours, C = 38 hours, and D = 44 hours after injection.

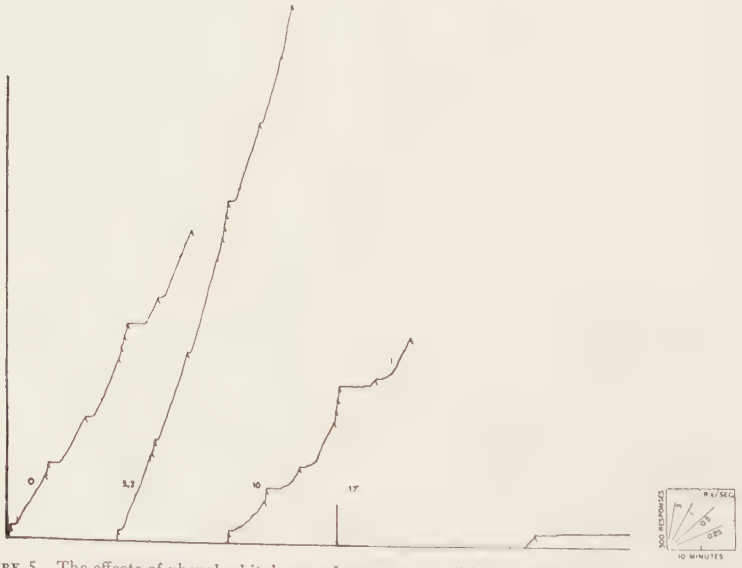

FIGURE 5. The effects of phenobarbital on performance on a different multiple schedule. Complete standard runs are shown, all starting 15 minutes after injection of the indicated dose (in milligrams).
Symbol: 0 = injection of saline alone.

tinuity of the record (third reward presentation, Record B ratios, FIGURE 4) caused by the pigeon continuing to peck the key straight through the period of food presentation.

Similar changes due to phenobarbital and to methamphetamine have been found in a series of experiments on birds working on a multiple schedule with different parameter values, that is, ratios of 30 and intervals of 5 minutes, and with a different sequence of ratios and intervals in the standard run. The effects of the drugs described do not seem to be crucially dependent on these arbitrarily chosen factors. Furthermore, in these experiments the birds were studied at a fixed time interval of 15 minutes following injection of graded doses of the drugs. The results confirmed that the sequence of changes at various time intervals following a single large dose of drug shown in Records A through D in FIGURES 3 and 4 are equivalent to those caused by graded doses of the drugs at a constant time interval (FIGURES 5 and 6).

Interval performance was more readily disturbed by both drugs than was ratio performance. Similar findings have been reported previously for pento-

FIGURE 6. The effects of methamphetamine. The arrangement is the same as that in FIGURE 5.

barbital.[1] This seems to be a rather general phenomenon. Interval performance is more readily disturbed by all significant variables than is ratio performance. On the other hand, the effects of phenobarbital and of methamphetamine on interval performance differ, as can be seen by inspection of FIGURES 3 and 4.

How may the behavioral effects of these drugs be analyzed?

Traditionally, behavioral effects of drugs are attributed to effects of the drugs on emotions such as fear and anxiety, and on ambitions, inhibitions, drives, and other hypothetical or arbitrarily defined "states." The system of experimentation under discussion leads logically to a different approach; it leads to an analysis in operationally defined terms. The pecking performance of the pigeons in these experiments in the absence of a drug depends on a number of explicitly defined variables, many of which are under direct experimental control. The state of food deprivation of the animal can be changed by simply changing the amount of food given. The size of the ratio and the length of the interval are under direct experimental control. The presentation of colored lights, correlated with schedule, comes to have an important effect on performance, and these stimuli can be changed. That rewards are contingent upon pecking has, of course, extreme importance in determining pecking performance. It is easy to arrange that pecks will no longer be rewarded (extinction). These are examples of some of the independent variables under the control of the experimenter that influence the dependent variable; that is, the rate of pecking. In analyzing the effects of a drug, the logical first step is to search for simple interactions between such factors and the effects of the drug; in other words, to determine to what extent the drug effects are "like" in the sense of having the same effect on behavior, the effect of change of level of deprivation, the change of size of ratio, extinction, and so on. Needless to say, this will only be the *first* step in the analysis of the effect of the drug, as will be pointed out later in this paper and in subsequent papers in this monograph.

First, are any of the effects of the drugs described above like the effects of changing the level of deprivation of the animal? Presumably, a drug effect of this kind would be like a sudden reduction in deprivation. Accordingly, experiments were done in which the birds were given free access to food for 15 minutes. The birds ate rapidly at first, but had stopped eating before the end of the 15 minutes. At various time intervals later, they were given the standard run. The bird whose performance is illustrated in FIGURE 7 gained 70 gm. in the 15 minutes of free feeding. In spite of this, the bird gave an essentially normal ratio performance 4 hours later (Record A, FIGURE 7) although some of the rewards were ignored. At much the same time, the interval performance was much disturbed, illustrating again the relative insensitivity of ratio performance. Of more interest is the nature of the disturbance of interval performance at 10 and 29 hours after free feeding. The sudden changes in rate are strongly reminiscent of the effects of methamphetamine and quite different from the effects of phenobarbital. On the other hand, feeding did not lead to a reduction in the initial pause, nor did it lead to an increase in total output of pecks except perhaps after 36 hours. Hence part, but only part,

of the effects of methamphetamine are like the effects of sudden reduction in deprivation. This is interesting in view of the well known "appetite-reducing" effect of methamphetamine in humans. The analogy cannot be sustained at the present time, however, since the effect of methamphetamine has not been shown to be specific to behavior maintained through food deprivation in the pigeons.

The effect of the drugs might mimic the effect of discontinuing rewards, that is, putting the birds on an extinction program. Accordingly, it was arranged that the food tray rose at the usual time called for by the schedule but the bird was prevented from eating by blocking the entrance to the tray. By the time the bird came to the 10 ratio, that is, when 5 rewards had been missed, the bird continued to peck straight through the (blocked) presentation of food (FIGURE 8). Also, the initial pause at the beginning of the interval tended to be reduced, often more strikingly than in this example, with a consequent general straightening out of the interval pattern also characteristic of drug effects. We may therefore tentatively suggest that a part of the effect of both methamphetamine and phenobarbital is due to a weakening of the behavioral control of the stimuli associated with reinforcement, similar to that obtained in extinction.

FIGURE 7. The effects of a period of *ad libitum* feeding on performance at various times later. Symbols: A = 4 hours, B = 10 hours, C = 29 hours, and D = 36 hours after feeding.

Other environmental factors whose modification might simulate the effects of drugs are the parameters of the schedule. As a matter of fact, for this *particular schedule*, change in the parameter value of the interval within wide limits causes only an orderly progressive change in the behavior, quite unlike the drug effects. Even considerable changes in the ratio value had no obvious acute effect on either the rate or pattern of pecking (FIGURE 9).

A final external control that will be considered is the effect of the 2 different key lights. Drugs might make the bird behave as though "it could not longer tell red from blue," to use loose phraseology. A study of this possible type of drug effect has already been completed on a different system and is in the literature.[2] In fact, a simple pair of stimuli like the red and blue lights used here seem to retain control even when the birds are under the effect of large doses of all the drugs studied to date. This phenomenon is evidenced by the normal ratio behavior in FIGURES 3, 4, 5, and 6 when the bird was definitely under the influence of the drugs. This finding is prima facie evidence for continued control by the red light. It seems that the drugs studied so far just do not have this kind of effect.

In conclusion, it has been possible tentatively to segregate out some of the

FIGURE 8. Selected interval and 10 ratios from the control run and from the run in which no rewards were given. Note the discontinuities in the record in ratio series in extinction caused by the bird continuing to peck through the period of the presentation of the "reward."

effects of phenobarbital and methamphetamine as being like the effects of change of some of the external controlling variables.

This discussion has been illustrative rather than exhaustive and conclusive. While it is suggested that this sort of simple analysis should be the first step in the analysis of the effect of a given drug, it is not suggested that all the effects of any drug will be expressible in terms of simple interactions with individual environmental variables. After all, most drugs affecting behavior act on the brain, and there is no reason why their effects there should coincide

FIGURE 10. The effect of changing the size of the ratio on the ratio performance. Even though the number of pecks required for reward has been increased suddenly as much as tenfold, the pigeon maintains a high standard rate without pausing at any time during the series of 10 ratios.

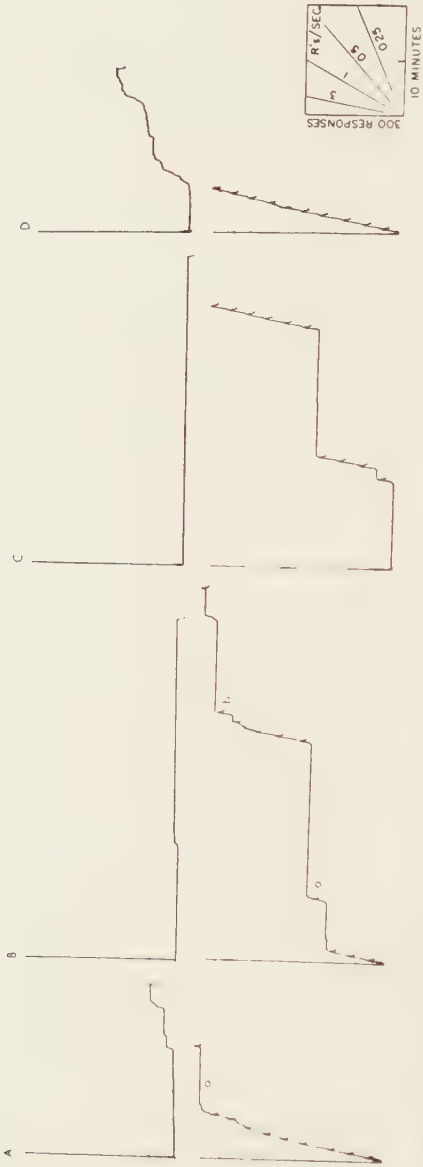

FIGURE 9. The effects of reserpine on performance at various time intervals after injection. The arrangement is the same as that in FIGURE 3. Symbols: A = 23 hours, B = 30 hours, C = 40 hours, and D = 48 hours after injection.

with the effects of any combination of external physical stimuli. Fortunately, the use of the free-operant technique for analysis of drug effects is not limited to analysis along the lines just discussed, as will be apparent below and in later papers in this monograph. The discussion has been limited to one type of schedule performance, purely in order to keep within reasonable bounds, but it is not a recommended procedure. Part of the extraordinary power of the free-operant technique results from the fact that it permits performances to be "tailor-made" in order to obtain optimum circumstances for manifestation of any specific aspect of a drug effect on which one wishes to focus attention.

The effects of reserpine on performance on the multiple schedule are instructive. Birds were given 100 μg. of reserpine intramuscularly. The drug effect developed slowly, reaching a maximum in about 1 hour. With this dose, pecking was abolished for about 18 hours. Recovery then proceeded progressively, as shown in FIGURE 10. The striking thing about these records are the long pauses in the ratios. The bird was physically capable of pecking at a high rate. The pecking started at a high rate, stopped abruptly, often for many minutes, and then it started again at the same rate. This effect was not peculiar to this particular pigeon, for it was seen in 5 of 6 pigeons given this dose, but has not been seen under any circumstances except following a drug. Increasing the size of the ratio, that is, the number of pecks required for a reward, from 60 to 250 or even more in the absence of a drug, does not engender a pause (FIGURE 9). In other experiments,* it has been shown that if a ratio is increased to 500-1000, then pauses do develop, but they occur characteristically directly following reinforcement before pecking has restarted. Once the bird had started pecking, it continued to do so, sometimes at an increasing rate, right on to reinforcement. This is quite different from the reserpine effect, in which the pauses come in the middle of the ratio as often as at the beginning. Again we may loosely compare this effect with the effects of reserpine described in humans. Reserpine liberates the pigeon from the normally powerful stimulus control of the red light just as it may liberate people from "tension" by reducing "obsessive-compulsive drives."[4]

In addition to the use of these procedures for analysis of drug effects, some exploration has been performed of their potential usefulness for screening purposes. For this use, it is necessary to be able to summarize the information contained in the cumulative record into a few simple numbers that will characterize as far as possible the different types of drug effect. The ratio performances have been used mainly as an indicator of the physical capabilities of the animal. While the ratio performance remains relatively normal it is safe to conclude that any changes seen in the interval performance are not due to the effects of a drug on the physical ability of the pigeon to peck. The obvious characteristics of the interval that are modified by drugs are (1) the total number of pecks made, and (2) the amount of pausing. Therefore, the pecks were counted on digital counters, and the total duration of pauses was recorded on clocks. The length of a pause was defined as the time beyond 10 seconds until the next peck. When performance is severely disturbed, the bird some-

*[See Morse & Herrnstein, this monograph, pp. 303-317.

TABLE 1

EFFECT OF DRUGS* ON INTERVAL PERFORMANCE

Drug	Dose (mg.)	No. of birds	Total pecks†	Pausing†	Prop. of pecks before pause
Methamphetamine	1	6	1.22	.74	0
Methamphetamine	3	2	1.53	1.68	.26
Pipradol	3	2	2.08	.36	.16
Methyl phenidylacetate	1	2	1.18	.62	.01
Methyl phenidylacetate	1.7	2	1.31	.77	.01
Methyl phenidylacetate	3	2	1.62	.66	.12
Phenobarbital	10	8	.97	1.01	0
Phenobarbital	17	7	.57	1.66	0
Glutethimide	30	2	.24	2.00	0
Methyprylon	17	5	.90	1.75	0
Methyprylon	30	2	.92	.53	.02
Chlorpromazine	3	3	1.42	.82	.13
Chlorpromazine	10	3	.52	1.03	.03
Chlorpromazine	17	7	.43	1.70	.01

* The drugs used in these studies were kindly supplied as follows:
Methamphetamine as Methedrine by Burroughs, Wellcome & Co., Tuckahoe, N. Y.; pipradol as Meratran by Wm. S. Merrell Co., Cincinnati, Ohio, methyl phenidylacetate as Ritalin by CIBA Pharmaceutical Products, Inc., Summit, N. J.; glutethimide as Doriden by CIBA Pharmaceutical Products, Inc., Summit, N. J.; methyprylon as Noludar by Hoffman-La Roche, Inc., Nutley, N. J.; and chlorpromazine as Thorazine by Smith, Kline & French Laboratories, Philadelphia, Pa.
† As proportion of control.

times fails to pause even at the beginning of the interval. In order to detect this effect, the pecks that occurred in the interval, before any pause of 10 seconds or more had occurred, were counted separately. The value of 10 seconds was chosen as being considerably shorter than the normal initial pause in the interval and longer than the interresponse times once the animal had started pecking.

Some results are shown in TABLE 1. The "total pecks" column permits the central nervous system stimulants (methamphetamine, pipradol, and methyl phenidylacetate) that led to more than the control number of pecks being made, to be distinguished immediately from the depressants (phenobarbital, glutethimide, and methyprylon) that led to fewer than the control number of pecks being made. There are many simpler methods available which will do this too, however. In general, as would be expected, the total time spent pausing increased as the decrease in total number of pecks made. The increase both in total pecks and in time pausing following administration of 3 mg. of methamphetamine necessarily means that the general rate of pecking between pauses must have been higher than normal. This phenomenon is a reflection of the sudden changes in rate described above. This dose of methamphetamine caused marked disturbance of normal behavior patterns, as is evidenced by 26 per cent of pecks occurring before a pause (control values are uniformly 0). A useful measure of the potency of stimulant drugs would be in terms of how much "pure" stimulation, that is, increased total output of behavior, can be obtained before the normal patterns are disturbed.

On the average, phenobarbital tended to cause reduction in total pecks and increase in pausing, although in many individual intervals there was virtually no pausing. This effect is even more marked with methyprylon. Following

a dose of 30 mg. the effect was sufficiently consistent to cause a decrease in average pausing. The 3-mg. dose of chlorpromazine caused a decrease in pausing, but it also caused an increase in total pecks and in pecks before a pause, just as a stimulant does. Higher doses caused changes like those caused by phenobarbital. The effects are obviously complex.

In short, the screening procedure shows indications of having considerable power to discriminate between different kinds of drugs affecting the central nervous system.

Before concluding, 2 criticisms of the general method will be mentioned. The first is that it is not always easy to translate the results into the traditional language used in the description of behavioral effects of drugs, the language of emotions, inhibitions, and so on. This limitation may, in fact, be an advantage. The traditional terms are notoriously ill-defined, and have led to a tendency to speculate rather than to design new experiments to obtain more facts.

The second criticism is that the dependent variable, the rate of pecking, is only a tiny fragment of the total behavior of the animal. Whatever validity this criticism may have from the immediately practical standpoint of discovering new drugs, it seems to be quite invalid from the standpoint of basic research. We do not accuse biochemists of triviality when they attempt to isolate pure enzyme systems, although any 1 such system is only a tiny fragment of the total biochemical machinery of the cell. A detailed analysis is a prerequisite of a worthwhile scientific synthesis.

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DRUG-BEHAVIOR INTERACTION

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It is a common clinical observation that a given drug will display great variability in its behavioral effects not only from individual to individual but in the same individual at different times. Such variability often can be traced to the cumulative effects of the drug itself; that is, repeated doses sometimes result in greater tolerance, and sometimes they result in greater susceptibility to the drug. When such factors are not demonstrable, the usual recourse is to ascribe the observed variability to unidentified physiological fluctuations.

In recent years, however, it has become evident that a hitherto-neglected set of variables contributes powerfully to the uncertain behavioral consequences of drug administration. These variables, broadly described, are the relations between behavior and its controlling environment. Drug effects are dependent not only on the physiological state of the organism, but also on the environmental contingencies that are maintaining its behavior at the time.[1] Such contingencies vary tremendously, both qualitatively and quantitatively, among individuals and for a given individual at different times.

With the development of techniques that permit a high degree of experimental control over the behavior of the individual it has become possible to identify and explore many of the contingencies that generate behavioral processes.[2-4] The techniques developed independently of pharmacologic applications have yielded, in their recent extension to this area, a wealth of data on interrelations between drugs and behavior. In fact, a new kind of problem has arisen. Having made the point that drugs and behavior are interactive, the young science of psychopharmacology (or pharmacopsychology, depending upon in which of the 2 fields one's major interest lies) faces the formidable task of systematizing the observed relations into an empirically sound and rational classification. While the present paper does not pretend to offer any such classificatory scheme, it is hoped that the data to be presented will emphasize the need for such an undertaking and will perhaps supply some useful leads.

Differential Reinforcement of Low Rates: Amphetamine, Alcohol, and Sodium Pentobarbital

One relatively simple contingency that is sensitive to pharmacologic manipulation generates a form of behavior that has been termed "spaced responding,"[5] or "timing."[6] "Differential reinforcement of low rates" (DRL), more descriptive of the actual contingency, is a term adopted at the Harvard Psychological Laboratories, Cambridge, Mass., and will be used here.

The subjects, albino rats in this case, are first placed on a water-deprivation schedule on which water is available to them for 1 half-hour at the same time each day. Dry food is always available except during experimental sessions. These sessions run for 2 hours just prior to the normal watering time. After the drinking rhythm has been established, the animals are placed in a chamber

containing a lever and an apparatus that delivers a small drop of water each time the animal presses the lever. Lever pressing may be "shaped up" according to the procedure described by Skinner,[2] or the animal may be left to his own devices. In either case, the DRL contingency is introduced after the animal has pressed the lever 100 times and has received 100 water rewards (reinforcements).

In the DRL procedure, the animal must space his responses in time if he is to secure a drop of water. For example, on a 20-second DRL, used throughout these experiments, a lever press produces a reinforcement only if 20 seconds or more have elapsed since the preceding response. If a response occurs too soon, the DRL timer is reset and the timing interval begins anew.

A direct measure of the behavioral adaptation to this contingency is provided by the relative-frequency distribution of time intervals between successive responses (interresponse times). These interresponse times are shown in FIGURE 1, which illustrates the development of spaced responding by 3 rats. In the first session the distributions are roughly similar to those expected on the basis of "random" responding.[7] During the second session the DRL contingency shows a clear effect upon response spacing. The behavior gradually becomes more efficient, and the distributions reach their final form at least by session 25 (after 50 hours). The high proportion of "bursts" of responses, as indicated by the large number of interresponse times of less than 2 seconds, is typical of this procedure, and it has not yet received a satisfactory explanation. With the exception of these bursts, the peak frequency is usually located between 18 and 20 seconds, just short of the required interval, although an occasional animal displays a more appropriate peak between 20 and 22 seconds.

Some effects of amphetamine and alcohol upon the DRL interresponse time distribution have been reported elsewhere.[6] Amphetamine moves the peak of the distribution toward shorter interresponse times. That is, the animals tend to respond too soon under the influence of this drug. Alcohol does not affect the location of the peak, but it flattens the distribution slightly because of a small increase in the frequency of very long pauses between responses.

The relative-frequency distribution of interresponse times does not provide us with any information about the time course of the drug action or about the total behavioral output. Such information is contained in the cumulative response curves "drawn" by the animals. FIGURE 2 illustrates a normal DRL curve and another curve produced following an intraperitoneal injection of amphetamine (approximately 3 mg. kg.). The upper curve demonstrates the over-all stability of the DRL base line, while the lower curve shows the behavioral output gradually reaching a maximum level under the influence of amphetamine and beginning to fall toward the end of the session as the drug wears off.

In FIGURE 3, a 1 gm./kg. dose of 10 per cent ethyl alcohol is seen to produce a decline in output, with relatively long periods of no responding interspersed among periods of normal rates. Again, a continuous picture of the drug's time course is provided by the cumulative record.

In FIGURES 2 and 3 we have seen 2 drugs, alcohol and amphetamine, displaying nearly opposite effects upon the same type of behavior. It is not

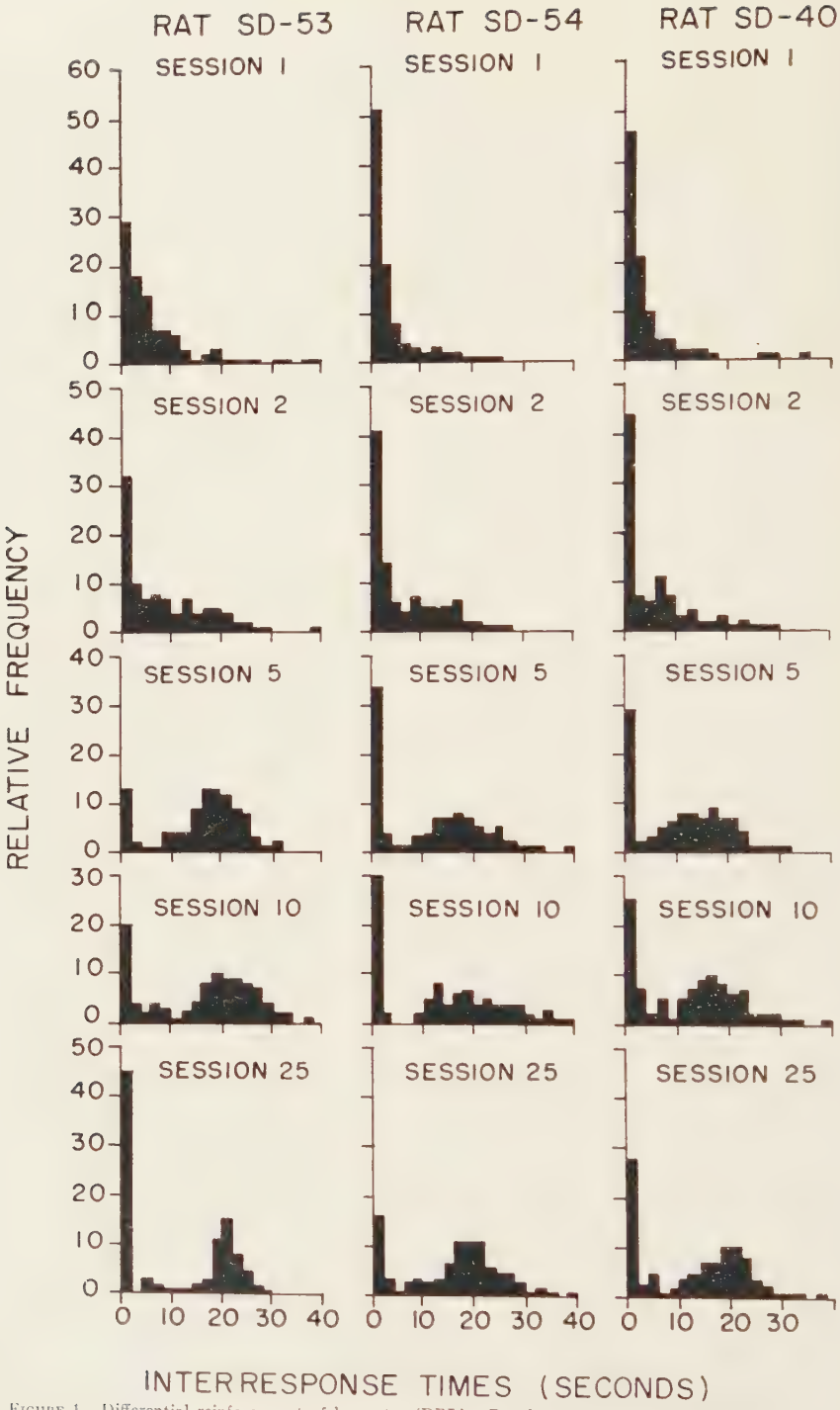

FIGURE 1. Differential reinforcement of low rates (DRL). Development of the temporal discrimination

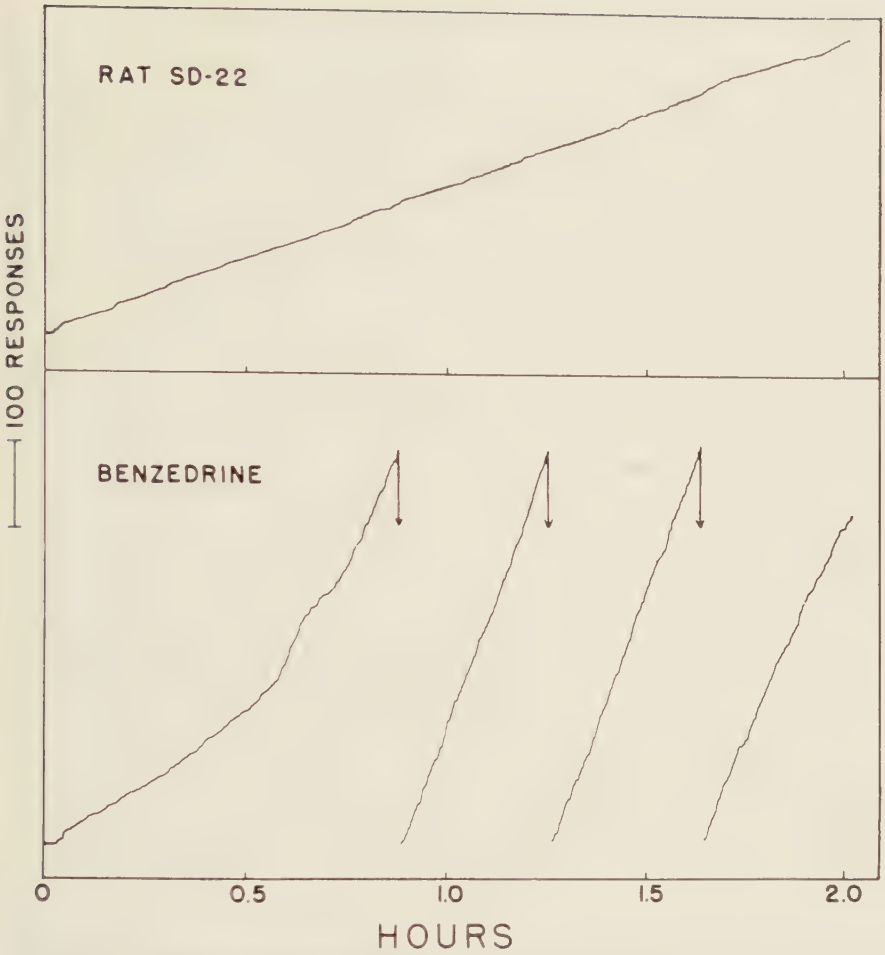

FIGURE 2. Cumulative lever-pressing curves illustrating the normal rate and the effect of amphetamine on DRL-response.

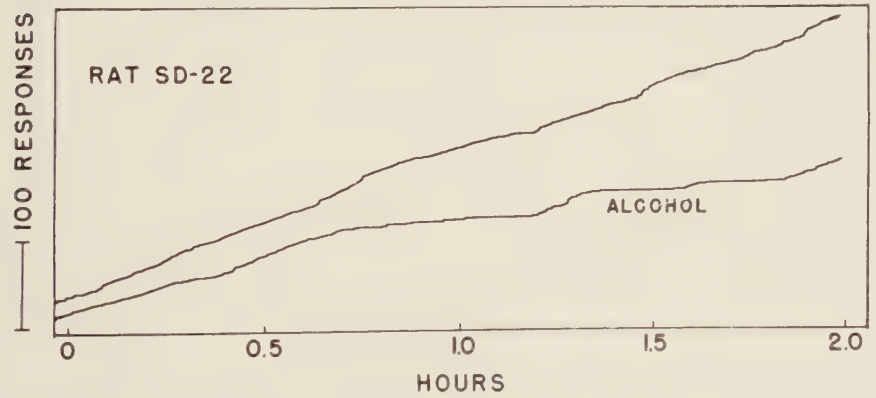

FIGURE 3. Cumulative lever-pressing curves illustrating the normal rate and the effect of alcohol upon DRL response.

necessary, however, that all effective drugs fall into 1 or the other of these 2 categories. Sodium pentobarbital, for example, in the proper dosage, depresses the total output, but does so in a quantitatively and qualitatively different fashion than does alcohol. An experiment was performed in which doses of 2, 4, 6, and 8 mg./kg. of sodium pentobarbital were injected. An effect was observed only with the highest of these doses, as illustrated in FIGURE 4. Here the interresponse-time distributions are presented together with their corresponding cumulative curves. The 8 mg./kg. dose produced behavior charac-

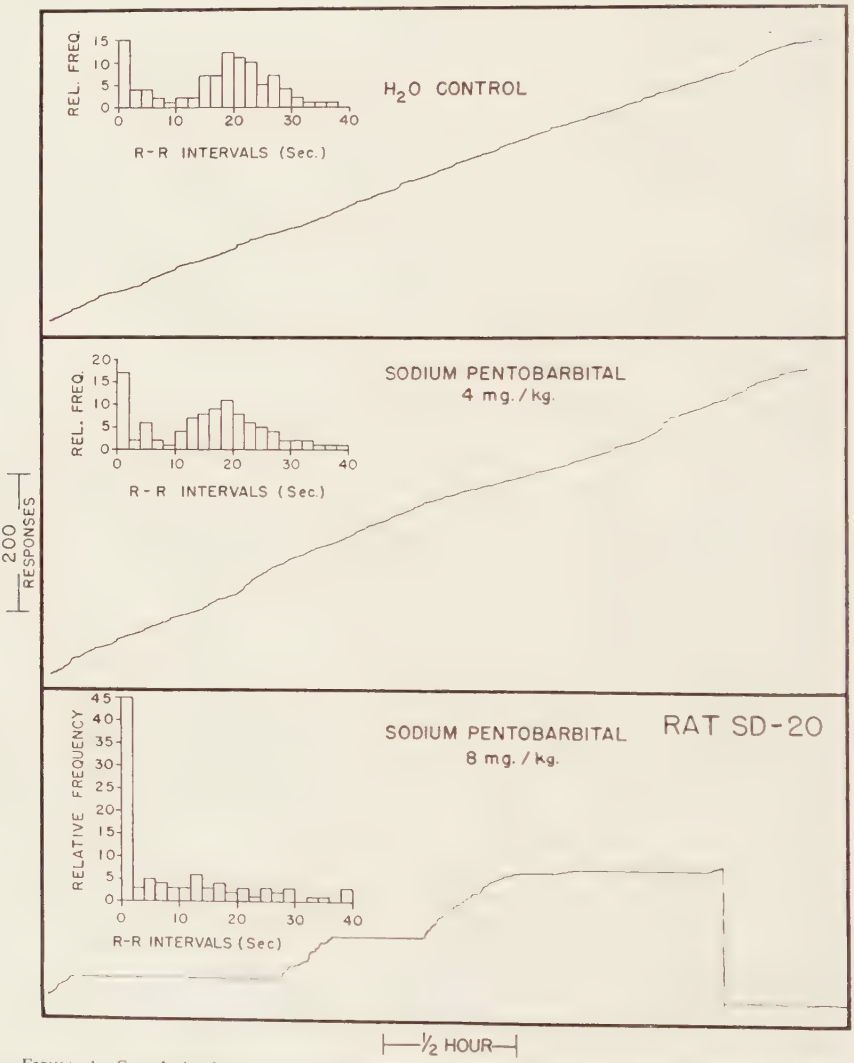

FIGURE 4. Cumulative lever-pressing curves and interresponse time distributions illustrating the effect of phenobarbital upon DRL response.

terized by alternating pauses and bursts of rapid responding. The bursts possibly correspond to the clinical observation of an excitatory state in the early stages of anesthesia. The interresponse-time distribution is markedly different from that observed after alcohol administration.[6] While the latter drug showed only a slight effect upon the distribution, sodium pentobarbital almost completely does away with all evidence of timing behavior. The distribution of interresponse times is nearly flat, with the exception of the increased proportion of rapid bursts of responses.

Combined DRL and Simple Discrimination: Amphetamine and Reserpine

In some of our DRL experiments, 2 levers are available to the animal. On 1 lever, the animal is reinforced according to the DRL contingency. That is, a response on the DRL lever produces a drop of water every time that 20 seconds or more have elapsed since the last response on that lever. The other lever produces a reinforcement only if it is pressed during the presence of an auditory stimulus. A reinforced response on this lever also terminates the stimulus, so that only 1 reinforcement per stimulus presentation is possible. Every 4 minutes the programming apparatus is "conditioned" in such a way that the next 3-second pause after a response on the DRL lever will produce the stimulus. Thus the stimulus, when it appears, always follows a DRL response by 3 seconds. This program was arranged to minimize interaction effects between the 2 levers.[8]

With this procedure, simultaneous auditory and temporal discriminations are built into the animal's behavioral repertoire. Under such conditions the DRL behavior is typical of that already described. When the auditory stimulus is presented there is usually a quick response on the second lever, with few "extra" responses on this lever in the absence of the stimulus. The frequency of such extra responses, along with the latency of the appropriate response in the presence of the stimulus, form the 2 principal measures of the auditory-stimulus discrimination.

When amphetamine is administered to animals working under the dual contingency, the usual effect upon DRL responding is observed; that is, the response rate increases, and the modal interresponse time shifts to a lower value. The amphetamine effect, however, is not confined to the timing behavior. The animals also display a substantial increase in output on the stimulus-discrimination lever. Although there is no decrement in the latency of response to the auditory stimulus, the animals press the second lever more frequently when the appropriate stimulus is absent. This indicates that the effect of amphetamine is not confined to temporal discriminations alone. There is evidently a more general effect upon several classes of discriminations.

A relation of a different order has been found between reserpine and behavior controlled by these contingencies. Two rats working on the combined DRL-stimulus discrimination procedure were given daily intraperitoneal injections of reserpine in doses of 0.2 mg./kg. The injections were given within 1 to 4 hours *after* each experimental session. One animal showed no effects of the drug treatment. The data for the second animal may be seen in FIGURE 5,

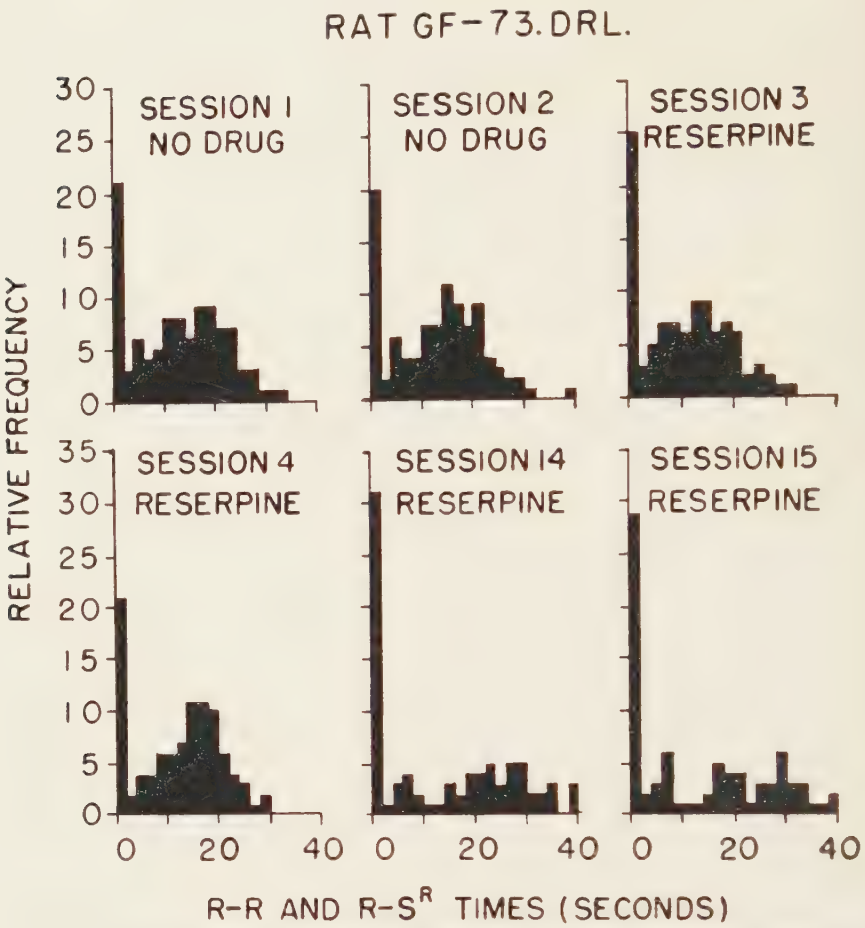

FIGURE 5. Interresponse time distributions illustrating the differential effect of reserpine upon temporal and stimulus discriminations.

in which no striking effect appears until the animal has been on the drug regimen for 2 weeks. At this point the temporal discrimination displays marked deterioration. Unsystematic observation of the animal's normal activity and his reactions to handling did not reveal any changes. The stimulus discrimination also appeared relatively unaffected with respect to the frequency of extra responses on the stimulus lever and the latency of responses to the stimulus. The latency measure is actually reflected in the distributions of FIGURE 5. These distributions include not only response-response (R-R) intervals, but also response-reinforcement ($R\text{-}S^R$) intervals, regardless of which lever produced the reinforcement. Since the stimulus occurred 3 seconds after a response on the DRL lever, short-latency responses on the stimulus lever recorded an $R\text{-}S^R$ time of 3 to 6 seconds. These responses usually show up in the control and early drug sessions as a minor peak in the distribution be-

tween 4 and 6 seconds. This peak is especially prominent during sessions 14 and 15, when the virtual elimination of short DRL interresponse times makes the R-S^R intervals stand out. Thus we see reserpine, unlike amphetamine, producing a differential effect upon time and stimulus discriminations. The different result observed in the 2 animals is probably a matter of dosage, as will be indicated in data presented below.

Avoidance Behavior: Amphetamine and Reserpine

We have seen some effects of several drugs upon behavior controlled by a specific reinforcement contingency. The type of behavior generated by this contingency was labeled "timing." One drug, amphetamine, acted similarly upon behavior under temporal control and behavior controlled by an auditory stimulus. Another drug, reserpine, showed a differential interaction with the 2 contingencies. Both forms of behavior were under appetitive control. That is, the programmed contingencies set up the conditions under which thirsty animals could secure water. The question arises as to whether drug-behavior interactions may be classified along the lines of appetitive versus aversive techniques of behavioral maintenance. This question becomes especially important with respect to the new "tranquilizing" drugs.

One technique of aversive control that we have employed generates a stable rate of avoidance behavior and, at the same time, permits the investigation of temporal discrimination. As with the appetitive techniques, the animals are placed in a chamber containing a lever. Brief shocks are delivered to the animal through the grid floor of the cage. Both the lever and the walls of the cage must be included in the shock circuit, or else many animals will develop avoidance behavior of a different topography than the pattern that our apparatus will record. The shocks are delivered at regular intervals; that is, every 20 seconds, unless the animal presses the lever. Every lever depression postpones the shock for another 20 seconds. Only the initial lever depression delays the shocks, and continued holding of the lever by the animal has no effect upon the time of shock delivery. If the animals do not acquire the avoidance response under these conditions, they may be helped along by decreasing the time interval between shocks whenever they fail to respond. That is, the "shock-shock" interval may be made considerably briefer than the "response-shock" interval.[4] A "shaping" process similar to that used with positive reinforcement may also be employed. That is, the class of behavior that will postpone the shock may be restricted gradually by the experimenter until the behavior finally includes only movements that succeed in depressing the lever.

FIGURE 6 depicts an example of relatively rapid acquisition of the lever-pressing response under conditions in which the shock-shock and response-shock intervals are both 20 seconds. The rate is relatively stable and ready for use as a base line by the twelfth session (after 72 hours). Typical stable states are shown for 3 animals in FIGURE 7. The number of hours required to achieve stability, and the rates of responding in the final state, may vary considerably from animal to animal, but a given subject may be depended upon to produce consistent behavior from session to session.

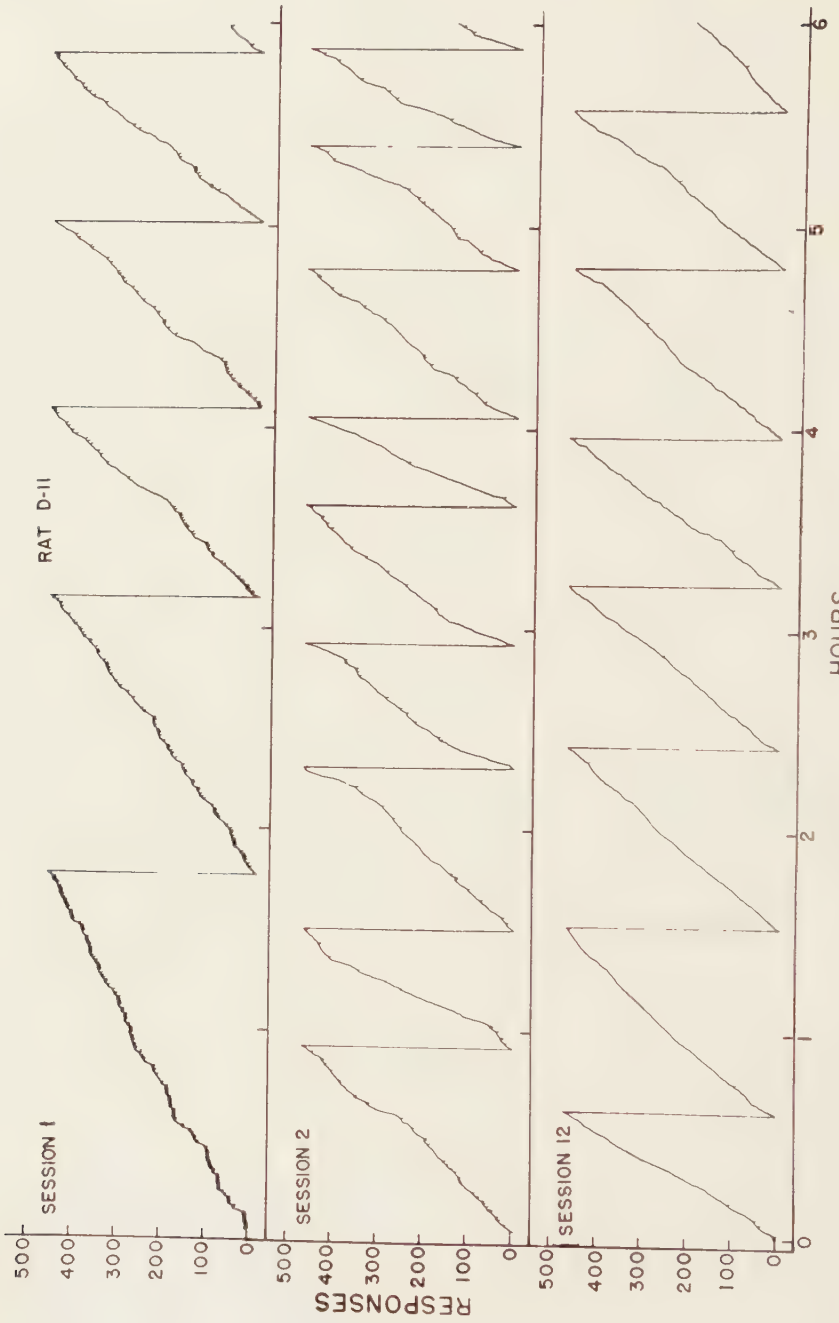

FIGURE 6. Cumulative lever-pressing curves illustrating the acquisition and steady state of avoidance behavior. The oblique "pips" on the record indicate shocks.

As with the DRL procedure, we may also record relative frequency distributions of time intervals between successive avoidance responses. Although we have shown elsewhere that the avoidance responses need not be temporally spaced in a manner indicating time discrimination, such spacing does occur to a greater or lesser extent with continued training,[10] and the process may be facilitated by special procedures.[11] Distributions indicating a timing process were utilized in the experiments described below.

In the upper frame of FIGURE 8 is an interresponse time distribution fairly typical of those observed after a time discrimination has become well-established. The only atypical feature of this distribution is the absence of the usual high frequency of rapid bursts. It will be noted that the interresponse times gradually rise to a maximum frequency shortly before a shock is due.

When this animal was given a 3 mg. kg. dose of amphetamine, the rate of avoidance responding increased and the time discrimination was affected in much the same way as in the DRL procedure. The intervals between responses became shorter, with the maximal effect showing up within the first hour (FIGURE 8). The effect diminished slightly during the second hour, and the behavior returned to an approximately normal state after 3 hours. We observe, then, that the effect of amphetamine on timing is not confined to behavior under appetitive control but extends also to the avoidance situation. Similar results have been reported by Milner,[12] who used a somewhat different avoidance technique.

In the experiments in which reserpine was used, the avoidance procedure was slightly modified in that an intermittent-shock schedule was employed. The "100-per cent shock" schedule was the same as that described above. Each time the animal waited 20 seconds without pressing the lever, a shock was administered. In the "20-per cent shock" schedule, however, the animal did not receive a shock *every* time 20 seconds elapsed without a response. Instead, the shock occurred only on 20 per cent of the occasions on which it was "due." That is, for every 5 times, on the average, that the animal waited 20 seconds, it received one shock. With the animals employed in these studies, it had previously been found that a 20-per cent shock schedule, with no drug, produced about the same response rate and interresponse-time distribution as did the 100-per cent shock schedule.[13]

Two rats were given 0.2 mg. kg. doses of reserpine following each 6-hour avoidance session. The response rates declined rapidly in both cases, but as 1 of the animals became ill and subsequently died, we present only 1 set of data in FIGURE 9. It may be seen that the rate declined steadily on the 20-per cent shock schedule, but that the peak interresponse time was relatively unaffected until the rate became so low that the distribution could not be considered reliable. In session 6, when the shock schedule was changed to 100 per cent, we see a hint of an interesting drug-behavior interaction. The more demanding schedule seemed to produce a slight amelioration of the reserpine effect, in that there was an increase in rate and some indication of a return of the timing behavior.

This effect was followed up more systematically with 2 animals and with a

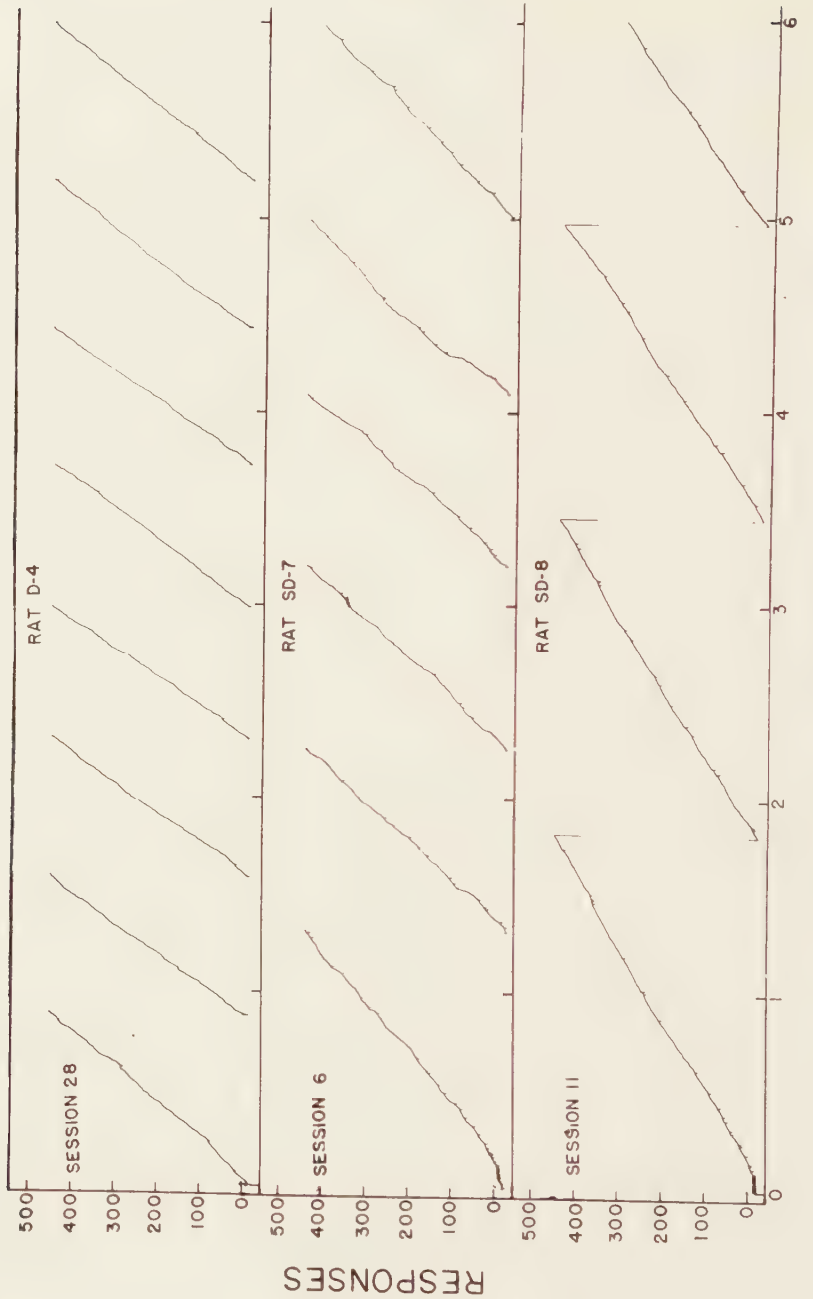

FIGURE 7. Cumulative lever-pressing curves illustrating avoidance behavior in the steady state. The oblique "trips" on the record indicate shocks.

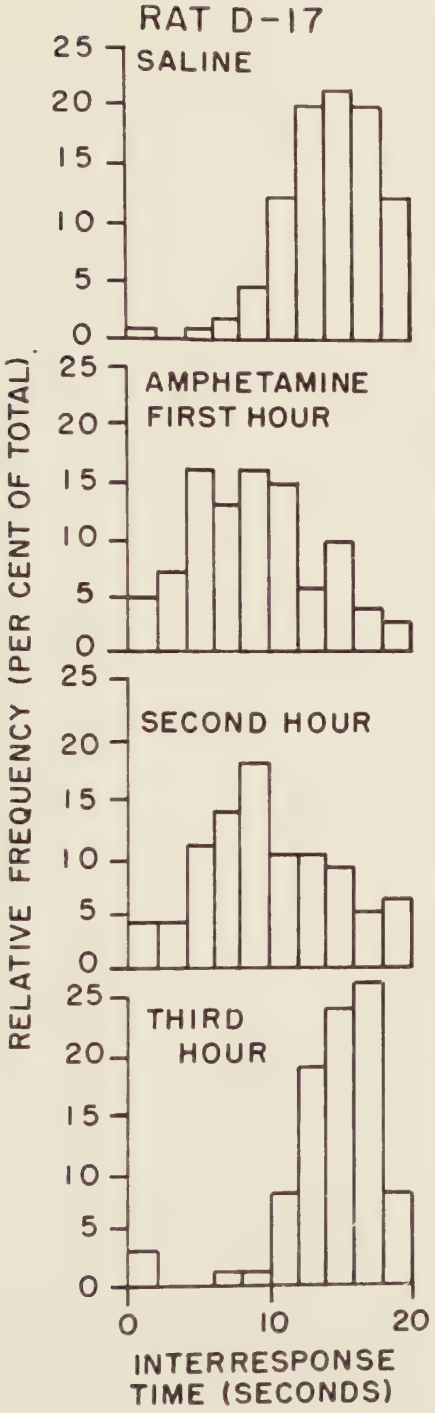

FIGURE 8. Interresponse time distributions illustrating the effects of amphetamine upon avoidance behavior.

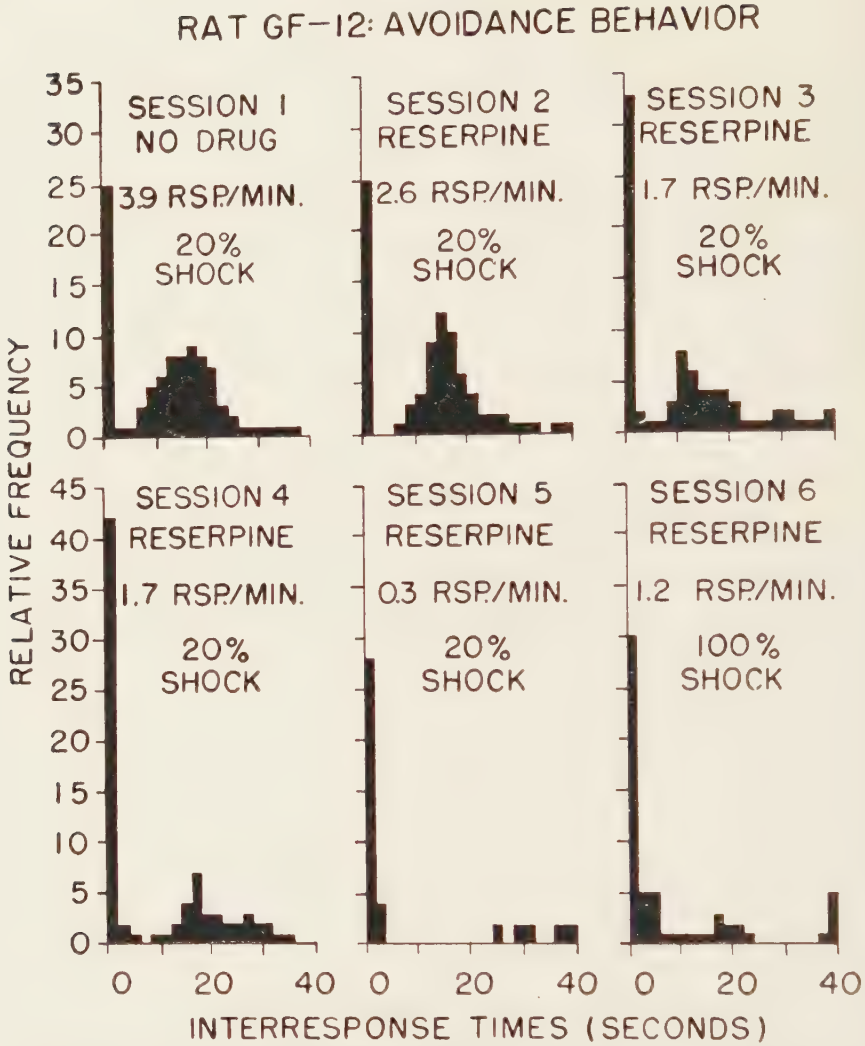

FIGURE 9. Response rates and interresponse time distributions illustrating the effects upon avoidance behavior of a 0.2 mg./kg. daily maintenance dose of reserpine.

reserpine dose of 0.1 mg., kg., one half of the dose used previously. In FIGURE 10 are presented the rate data for 1 of these animals. Here again may be seen a steady decline in rate of avoidance responding on the 20-per cent shock schedule during the period of drug administration. Each time the 100-per cent shock procedure was introduced, however, the rate of responding rose to its normal level. Changing the shock contingency eradicated the drug effect even though, in the *untreated* animal, the 2 shock schedules showed no differential effects.

In the case of the second animal, there was an even more intriguing effect. FIGURE 11 again demonstrates a difference in rate of avoidance behavior be-

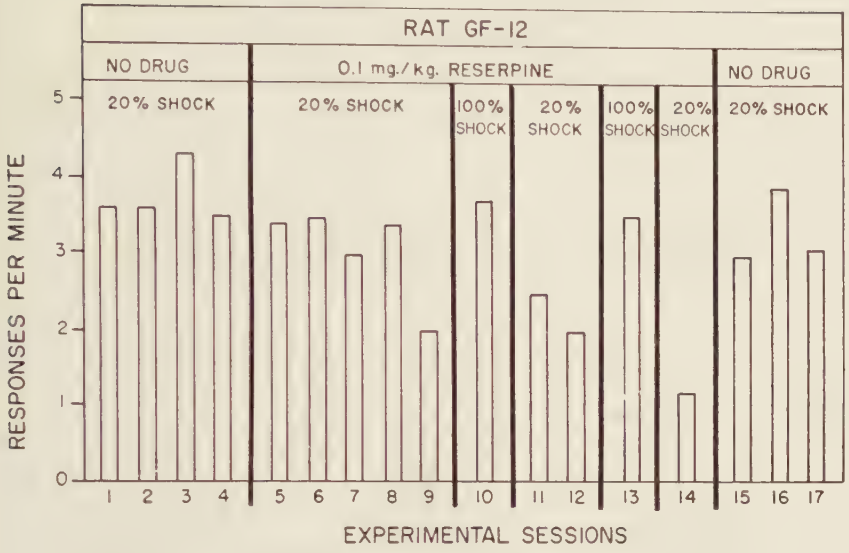

FIGURE 10. Rate of avoidance as a joint function of reserpine and shock schedule.

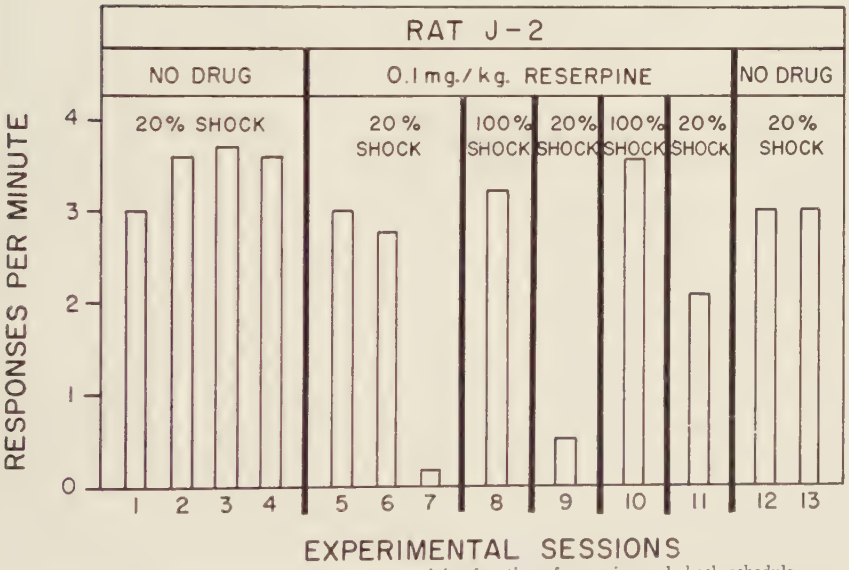

FIGURE 11. Rate of avoidance response as a joint function of reserpine and shock schedule.

tween the 20- and 100-per cent shock schedules, but in this case there actually appears to be a gradual recovery even on the 20-per cent shock contingency. Here we have the possibility, which deserves more complete exploration, of a "therapeutic" effect extending from behavior governed by 1 contingency to behavior governed by another.

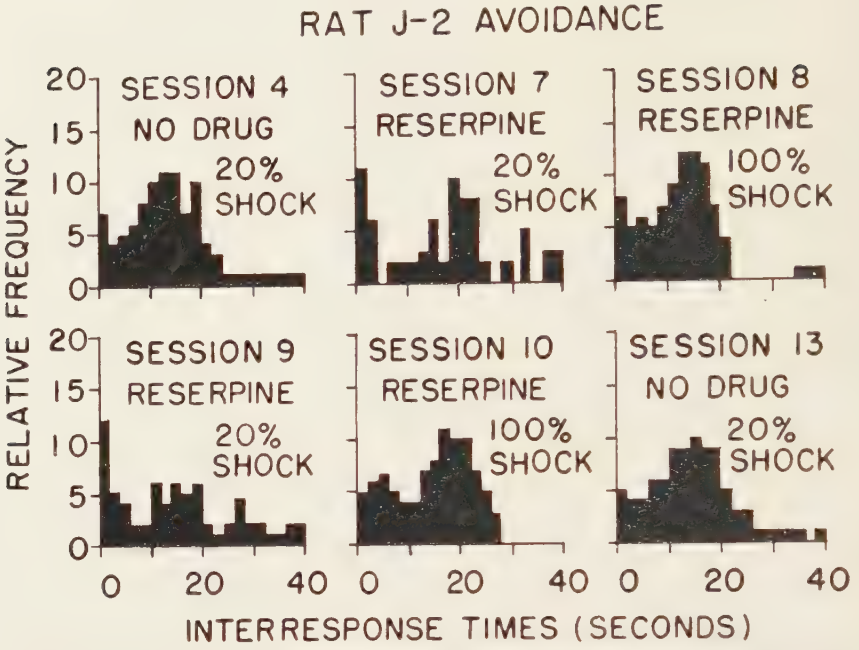

FIGURE 12. Interresponse time distributions as a joint function of reserpine and shock schedule. Session numbers correspond to those of FIGURE 11.

Interresponse time distributions corresponding to the rates shown in FIGURE 11 may be seen in FIGURE 12. Although the 20-per cent shock distributions under reserpine are somewhat more irregular than the controls because of the low output, the peaks remain fairly stable throughout the reserpine sessions, indicating again a differential effect of reserpine upon the rate of avoidance responding and the temporal discrimination.

Conditioned Suppression: Reserpine

In the DRL experiments, both the response rate and the temporal discrimination were relatively resistant to a fairly high dose (0.2 mg. kg.) of reserpine. In the avoidance situation, however, reserpine displayed a relatively rapid effect upon the response rate, even with the dose cut in half (0.1 mg. kg.). The temporal discrimination, however, remained resistant to the drug. The possibility arose, therefore, that the effects of reserpine were actually specific to behavior maintained by aversive contingencies, with a minimum of "side effects." The next step was to administer the drug to animals working in a different type of aversive situation.

The technique was adapted from one originally used by Estes and Skinner,[14] and recently investigated in greater detail by Brady and Hunt[15] and by Azrin.[16] The animal used in this case was a rhesus monkey, who pressed a lever on a variable-interval schedule for a reward of sweetened orange juice. The conditioned suppression, or "anxiety" response, was superimposed upon the

variable-interval base line in the following manner. Every 5 minutes an auditory stimulus (clicking noise) was introduced, remaining for 5 minutes. The termination of the stimulus was sometimes accompanied by an unavoidable shock, delivered through the grid floor. One third of the stimuli in each session were paired with the shock in mixed order. During each stimulus presentation it was still possible for the animal to secure the orange juice on the same variable-interval schedule that was in force in the absence of the stimulus.

The behavioral effects of the stimulus-shock pairings may be seen in the upper cumulative curve of FIGURE 13. Between stimulus presentations, the monkey worked at a fairly stable rate. Shortly after each stimulus onset, however, the animal's normal lever-pressing behavior was completely disrupted. During the stimulus period, the monkey typically displayed agitated behavior, with periods of considerable activity such as violent shaking of the cage and rapid running and leaping about the cage, alternating with periods of complete immobility. Following the termination of the stimulus, the animal returned to its normal pattern of response.

Daily injections of reserpine were given following the experimental sessions or at corresponding times on days when the animal was not tested. A high dose (2 mg. kg.) was administered on the first day and, on successive days, the amount was gradually reduced to 0.5 mg. kg. On this regimen, the character of the animal's behavior changed in the manner illustrated by the lower curve of FIGURE 13. There was no longer a cessation of lever pressing during the "anxiety" stimulus. The animal pressed the lever at approximately his normal rate both between and during the stimuli.

Thus reserpine again demonstrates a differential effect upon those aspects of behavior maintained by an aversive contingency and those maintained by

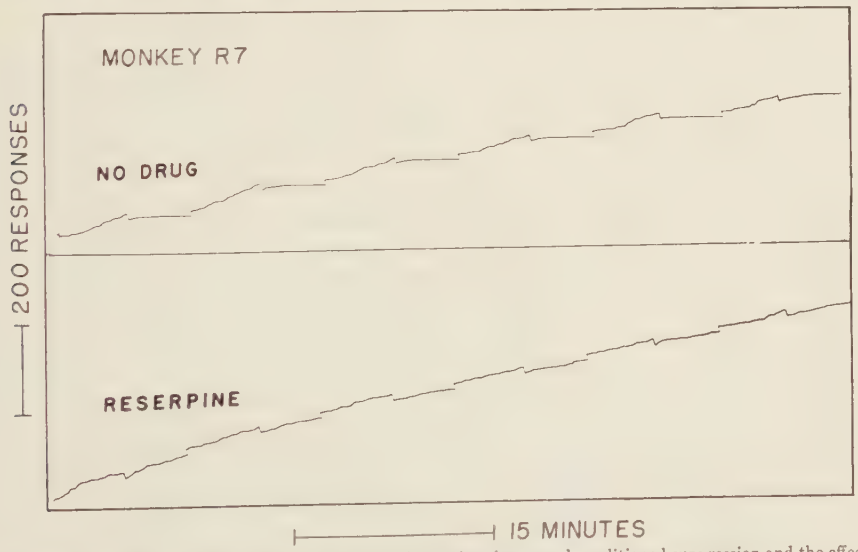

FIGURE 13. Cumulative lever-pressing curves illustrating the normal conditioned suppression and the effect of a daily maintenance dose of reserpine. Downward displacement of the curve indicates the stimulus.

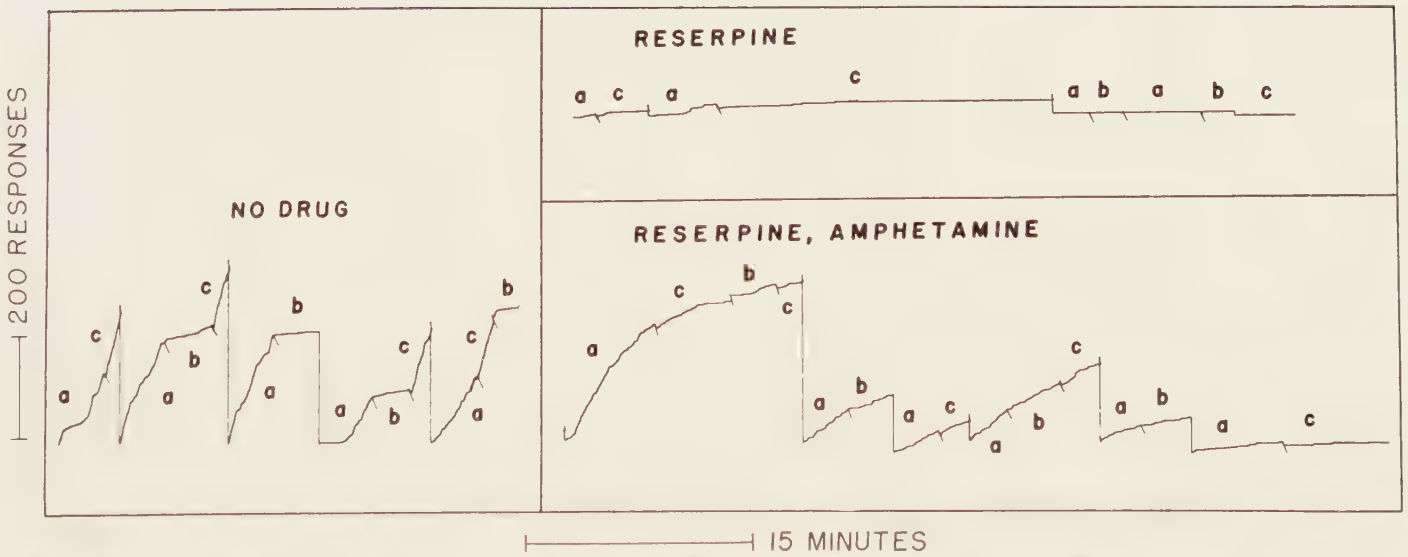

FIGURE 14. Cumulative lever-pressing curves illustrating the normal multiple-schedule performance, the effect of a large dose reserpine, and the effect of reserpine-plus-amphetamine. Behavior on the variable-interval schedule is indicated by *a*, DRL behavior by *b*, and fixed-ratio behavior by *c*. The recorder pen was reset at the start of each variable-interval period.

positive reinforcement. Similar results have also been reported with rats in the conditioned-suppression situation.[17] It may be noted, however, that while reserpine depressed avoidance behavior, it worked in the opposite direction in the "anxiety" situation. In this case we have a type of drug-behavior interaction in which a drug may either suppress or "rejuvenate" behavior, depending upon the nature of the variables currently maintaining the behavior.

Multiple Schedules: Reserpine

Unfortunately, the nice classification that seemed to be developing for reserpine on the basis of positive- and negative-reinforcement contingencies did not hold. This was brought out by means of the multiple-schedule technique developed by Ferster and Skinner.[18] In the multiple-schedule situation the animal works under 2 or more reinforcement schedules. Each schedule, however, is under stimulus control; that is, there is a different stimulus correlated with each reinforcement schedule. The animal learns to behave in accordance with the current schedule that is identified by the stimulus present at any moment.

The multiple schedule employed in this experiment involved 3 reinforcement contingencies. In the presence of a steady tone, the DRL contingency was in effect. Responses were reinforced only when 30 seconds or more had elapsed since the preceding response. When a clicking noise was presented, a fixed-ratio schedule was programmed. On this schedule, 10 lever presses were required for each reinforcement. When neither the tone nor the clicker was in operation, a variable-interval schedule was in effect in which responses were reinforced at irregular intervals, with a mean interval of approximately 30 seconds. The 3 schedules were programmed in a mixed order, and the duration of each stimulus was variable.

While the behavior at the time of reserpine administration was not as stable as might be desired, stimulus control of the behavior appropriate to each schedule was clearly evident, as may be seen in the left-hand curve of FIGURE 14. The letters refer to the schedule in effect in each portion of the curve. The variable-interval schedule is indicated by *a*, the DRL by *b*, and the fixed ratio by *c*.

A large reserpine dose of 1 mg./kg. almost completely depressed all lever-pressing behavior regardless of the reinforcement contingency. Subsequent reduction of the daily maintenance dose did not bring back the behavior that is depicted in its depressed state in the "reserpine" curve of FIGURE 14. When the animal began to show other generalized effects of the drug, such as loss of weight, flaccidity, and sluggishness, a 2 mg./kg. dose of amphetamine was administered just prior to the next experimental session. As shown in FIGURE 14 (lower right), amphetamine succeeded in bringing back lever-pressing behavior for a short time. There was, however, no differential behavior as a function of the reinforcement contingency. This may indicate that the reserpine had eliminated either the stimulus control, the schedule control, or both. On the other hand, this effect may be a consequence of the amphetamine, although a similar dose has been shown to sharpen, rather than to eliminate, stimulus control in the conditioned-suppression procedure.[17]

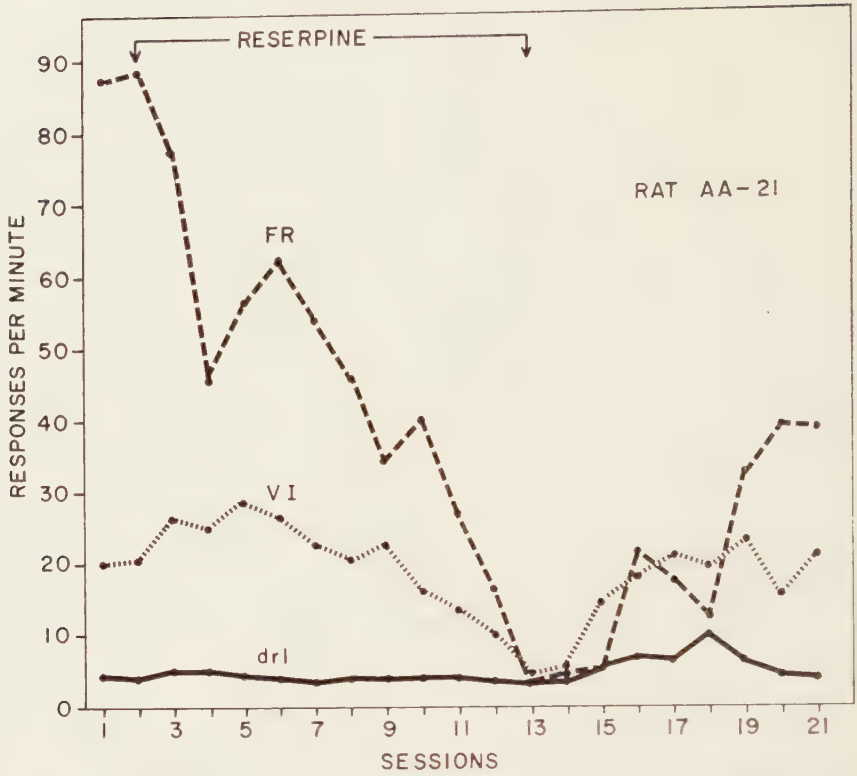

FIGURE 15. Response rates under each reinforcement contingency of the multiple schedule, illustrating the time course of action of a daily maintenance dose of reserpine of 0.1 mg./kg.

A more direct example of differential reserpine effects upon positive-reinforcement schedules was obtained by administering a lower dose, 0.1 mg. kg., in the multiple-schedule procedure. With this dose there was a clear depression of the fixed-ratio and variable-interval rates, while the DRL displayed a greater resistance consistent with the data presented above. The response rates on each of the 3 schedules are plotted session by session in FIGURE 15. The drug was administered daily, following each experimental run, after sessions 2 through 13. Not only is there a differential sensitivity of the behavior under the 3 schedules, but there is also a marked difference in the time course of action of the drug, depending upon the reinforcement contingency. Depression of the fixed-ratio behavior begins immediately, and the variable-interval behavior begins somewhat later, while the DRL behavior remained relatively stable throughout the drug treatments. This intimate relation between drug and reinforcement contingency continues into the recovery period where the variable-interval behavior returns to its base level well before the fixed-ratio behavior. The slight rise in the DRL rate following withdrawal of the drug had not been observed in the previous DRL-reserpine experiments. The temporary increase in the variable-interval rate during the early drug sessions, however, has been

observed consistently in conditioned suppression-reserpine experiments that employed a variable-interval base line.[19] It may be noted that the differential time course of reserpine action as a function of the reinforcement-maintaining schedule suggests that the effect of the drug is on the schedule control rather than on the stimulus control. Although the evidence is not conclusive, there seems to be no a priori reason to believe that the 2 auditory stimuli (fixed-ratio and DRL) would display such markedly different sensitivity with respect to each other and to the condition in which both stimuli were absent (variable interval).

Summary

The data presented in this paper serve to emphasize the interdependence of pharmacologic and behavioral variables. It is clear that the relations between drugs and behavior are a function not only of the drug but also of the conditions under which the behavior is generated. The evidence also suggests that while drugs and behavior interact differentially, it will be difficult if not impossible to find a drug whose effects are confined to 1 specific behavior-environment contingency. The common-sense distinctions that we are accustomed to make between different types of behavior do not suffice to establish a classificatory scheme. We have seen reserpine affecting both positively and aversively maintained behavior. Within this classification, we have seen differential interactions as a function of more specific behavior variables such as shock frequency and reinforcement schedules. Such behavioral variables not only help to determine the drug effect, but also influence the temporal course of the effect.

In the case of amphetamine we have found an effect upon timing behavior in both appetitive and aversive situations, yet evidence presented here and elsewhere[21] indicates that amphetamine has a more general effect than simply upon timing behavior. Alcohol and sodium pentobarbital also affect timing behavior, but they do so in a fashion different from each other and from amphetamine. Behavior is not only differentially affected by drugs, but it also may respond to drugs in qualitatively and quantitatively different ways. Avoidance behavior is suppressed by reserpine under appropriate conditions while presumably related behavior in an "anxiety" situation increases in frequency.

The techniques reported in this paper and elsewhere in this monograph that permit the elucidation of such interactions between drugs and behavior reveal simultaneously both their strengths and their weaknesses. As techniques, their strength is made evident by the multiplicity of relations whose existence they have revealed and by the many untapped areas that it is now possible to explore. It is difficult for the behavioral scientist to restrain himself from probing these areas where one can hardly fail to observe striking behavioral changes as a consequence of injecting some mysterious substance into the gut of an experimental animal. This fact points up the weakness of the techniques. In their present form, and with our current state of understanding of the behavioral phenomena generated by the techniques, the result of such probing will be little

more than a bewildering array of highly interesting but completely unsystematic data. A small amount of restraint in the form of systematic behavioral investigation *prior* to drug investigation cannot fail to bring some order into the accumulated facts of drug-behavior interaction. A search for relations, rather than differences, among reinforcement contingencies; the unification of principles of aversive and positive control; a more precise delineation and classification of behavioral variables; and the discovery of relations between behavior and other biological phenomena will lead inevitably to the elimination of a great deal of psychopharmacologic investigation that now seems exciting but is actually little more than aimless wandering when compared to future potentialities in this field.

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EFFECTS OF DRUGS ON CHARACTERISTICS OF BEHAVIOR MAINTAINED BY COMPLEX SCHEDULES OF INTERMITTENT POSITIVE REINFORCEMENT*

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Behavioral base lines with several reproducible properties are useful in investigating the effects of drugs on learned behavior. Differential drug effects on interrelated characteristics of behavior make possible detailed analyses of drug action. In addition, behavioral base lines with complex properties offer an advantage in that they are more sensitive to the effects of drugs than are simple base lines.

A simple base-line performance is generated by a fixed-ratio schedule in which an animal is reinforced each time a small, constant number of responses is emitted. Following reinforcement, the animal responds at a high, fairly constant rate until the next reinforcement. It has been frequently noted that performance under this schedule is refractory to drugs. The insensitivity of behavior maintained by small ratio schedules is reflected both in the need for using relatively large quantities of a drug in order to observe any change in behavior, and in the precipitousness with which the change occurs. Once the dose is made large enough to affect the animal's performance, a gross disturbance in motor coordination also takes place.

When used in a base line that contains other schedules of reinforcement, however, a fixed-ratio schedule becomes a valuable tool, that is, where the fixed-ratio performance may be viewed as a characteristic component of a more complex behavior. FIGURE 1 shows the insensitivity of small ratio schedules and the specificity of drug action upon the multiple characteristics of a complex behavior. This curve is a cumulative record of pecking responses for a single pigeon on a day when it received a 4 mg. dosage of sodium pentobarbital. The number of responses is on the ordinate, and time is on the abscissa. This pigeon was maintained at 80 per cent of normal body weight on a regimen of partial food deprivation. The short diagonal marks indicate the points at which the response was reinforced with food. The behavioral base line was a multiple schedule containing 2 component schedules of reinforcement. In the presence of 1 stimulus, the pigeon was reinforced on a small fixed-ratio schedule—the 50th response emitted after the onset of the stimulus was reinforced. In the presence of the other stimulus the schedule was a fixed interval—the first response emitted after 10 minutes from the onset of the stimulus was reinforced. The early portion of the record shows a typical performance. When the ratio component was present, the animal responded at a high constant rate. When the interval component was present there was a positively accelerated curve up to the reinforcement. Later portions of the figure make

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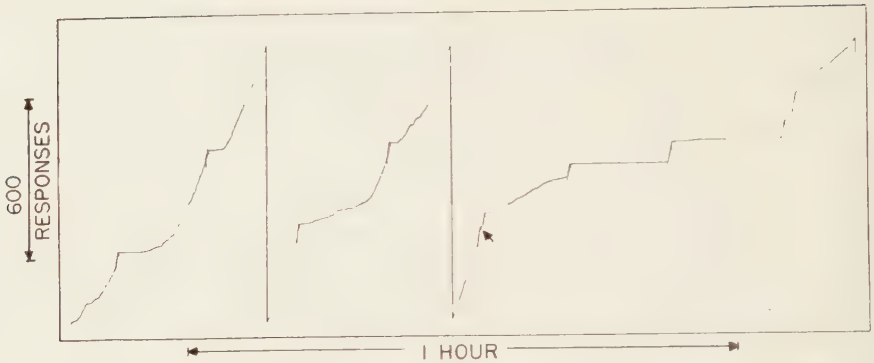

FIGURE 1. Cumulative response curve for a portion of a single experimental session. The schedule is a multiple fixed ratio (50) fixed interval (10). Reinforcements are marked by short diagonal strokes. Sodium pentobarbital (4 mg.) was administered intramuscularly to the pigeon at the point indicated by the arrow. (body weight—420 gm.).

it clear that the sodium pentobarbital disrupted the fixed-interval performance, but left the fixed-ratio performance intact. The effects were to a large extent duplicated when the fixed ratio and the fixed interval were studied in isolation.[1]

In FIGURE 1 the insensitivity of the ratio behavior can be regarded profitably as a control. It is clear that the drug has not simply acted on the animal's motivation or on the motor aspects of the response being studied, since the drug changes only 1 of 2 patterns of behavior that concurrently share a common response topography and the same conditions of deprivation. The drug is operating, in some way, on the behavioral processes that are responsible for the performance on the fixed-interval schedule.

The use of multiple schedules is a powerful technique for generating behaviors that are characteristically different. The animal responds appropriately to the schedule designated by the stimulus present. To obtain additional features in the base line one need only add new components to the complex-multiple schedule. As shown in FIGURE 1, the behavior patterns appropriate to the various component schedules remain essentially independent.

Schedules generating patterns of behavior with concurrently interacting characteristics provide especially desirable base lines for detecting the differential effects of drugs. An example of such a base line is also seen in FIGURE 1, in the fixed-interval performance before the injection of the drug. Several characteristics may be distinguished in each fixed-interval curve: a pause at the beginning of the interval; a region of positive curvature; a fairly constant terminal rate of responding; and the total number of responses emitted in the interval. Previous experiments have shown that sodium pentobarbital affects the various characteristics of the fixed-interval performance differentially.[2]

What we want to show in this paper is that, simply by arranging reinforcing contingencies within a single schedule, complexly interrelated behavioral characteristics can be created that are independent of any externally controlling stimuli. Some simple scheduling procedures (for example, the fixed interval) generate complex behavior, while other schedules (for example, fixed ratio) do not. The dependence of interrelated characteristics in a base

line upon reinforcing contingencies is conveniently shown by examining the behavior generated by modifications of the fixed-ratio schedule.

The performance under a small-ratio schedule is adequately described by specifying the rate of responding. An additional characteristic of ratio behavior emerges when the number of responses required for reinforcement is increased. Although animals will emit a substantial number of responses for each reinforcement, responding stops if the value of the fixed ratio is sufficiently great. The actual value that proves to be too great to maintain sustained behavior varies over about a ten-fold range, depending upon such factors as the previous history of the animal, the physical properties of the manipulandum employed, the conditions of deprivation, and the amount of reinforcement. If an animal is required to emit a number of responses somewhat smaller than the value at which responding ceases, the condition known as "ratio strain" develops.[3] Following a reinforcement, the animal does not respond for long periods. The major proportion of the responses is emitted at a high rate just prior to reinforcement. Between the pause and the high rate there are often some responses at a lower rate.

An example of a strained-ratio performance is seen in part *A* of FIGURE 2, which represents the first 2 hours of the daily 5½-hour session. This figure is a cumulative record of pecking responses for a pigeon whose schedule was a fixed ratio of 160 responses per reinforcement. In this figure the recording pen resets to the bottom of the record after each reinforcement. Periods of responding at high rates (5 responses per second) follow periods of no responding. In many instances (note especially the beginning of the reproduced segment) the pigeon emitted several responses before the high rate appeared. The performance exemplified here had been stable over a period of several months of daily experimental sessions. This pattern of no responding after reinforcement followed by responding at a high rate can be maintained indefinitely in animals that develop a strained-ratio performance.

Part *B* of FIGURE 2 shows a full 4-hour session that started 1 hour and 10 minutes after an intramuscular injection of 0.5 mg. of methamphetamine. The effect of the drug, which is detectable immediately from the start of the record, becomes more pronounced during the course of the session. The long pauses that normally follow reinforcements are greatly reduced. The drug has an excitatory effect in the sense that there is an increase in the number of reinforcements that the animal receives within the experimental session. In the local rates of responding, however, there is no increase. The rate of responding just prior to reinforcement is still approximately 5 responses per second. The high rates that appear in part *B* are not higher than those in part *A*. In fact, more responses are emitted at low and intermediate rates in part *B* than in part *A*. The base-line performance has been recovered in part *C*, which shows the first 2 hours of the session following part *B*. Again there are long pauses after each reinforcement.

In FIGURE 3 we see the effect of a larger dose of methamphetamine on the same pigeon. The strained-ratio performance generated by the fixed ratio of 160 is depicted in the 2-hour segment of the control record labeled part *A*.

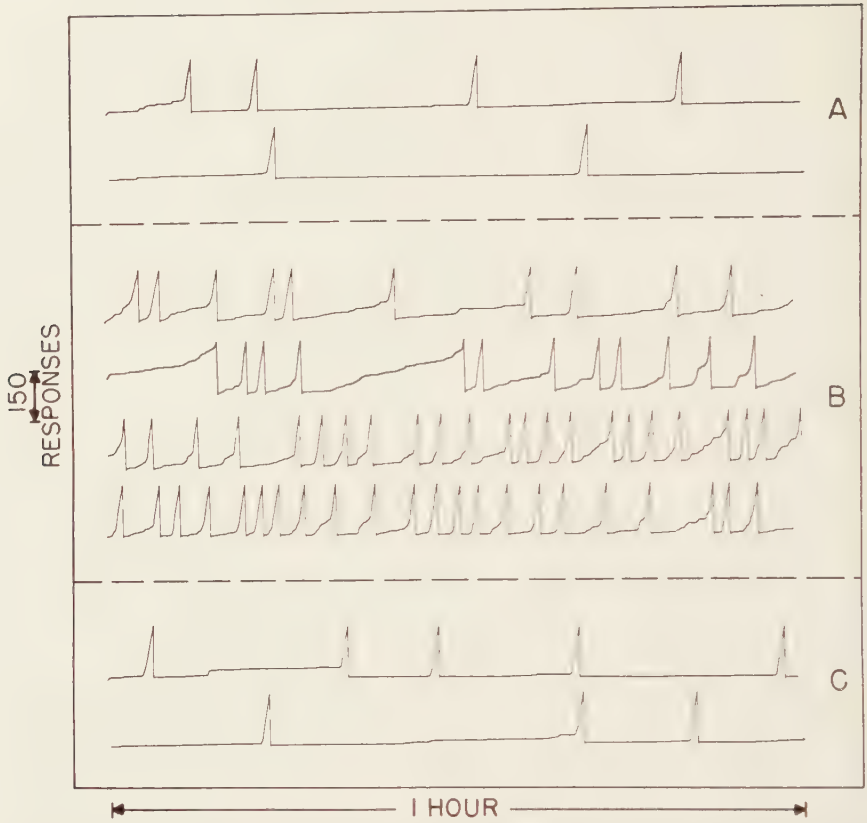

FIGURE 2. Cumulative response curves from 3 consecutive sessions (parts *A*, *B*, and *C*, respectively). The schedule is a fixed ratio (160). Reinforcements are marked by a resetting of the recording pen to the bottom of the record. Methamphetamine (0.5 mg.) was administered prior to part *B* (body weight—416 gm.).

Part *B* is a 7-hour experimental session immediately following the administration of 2 mg. of methamphetamine. This 7-hour session started 5½ hours after the segment shown in part *A*. As before, the pauses following reinforcement have disappeared. There is, in addition, another effect that was only suggested at the smaller dosage. The pigeon never responded at the high rates that appear in the control record. Although there was again an excitatory effect with respect to over-all output, the local rates of responding fell substantially below those observed in the absence of the drug. Although the rate of responding increased progressively throughout the 7-hour period, by the end of the session it was still lower than normal.

Part *C* of FIGURE 3 shows the beginning of the next experimental session (16 hours after completion of part *B*). Initially there is a clear residual effect of the drug. The rate has returned to normal, but the pauses following reinforcement are at first shorter than in the control performance in part *A*. This may be a direct effect of the drug, or it may be due to the fact that the animal received an unusually large number of reinforcements on the previous day.

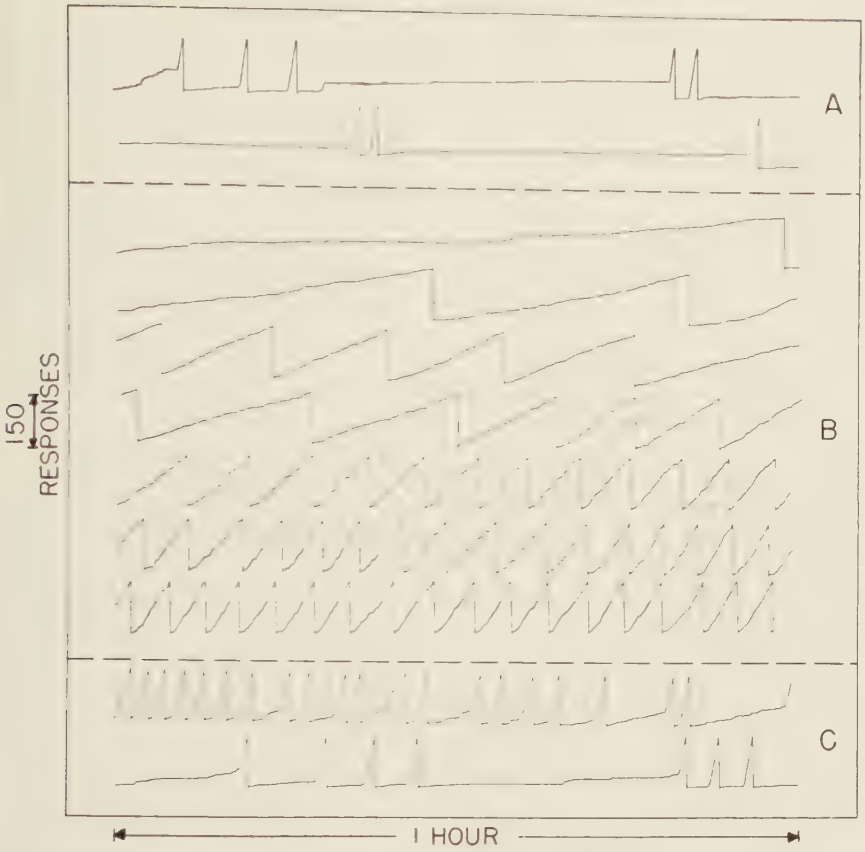

FIGURE 3. Cumulative-response curves from 3 consecutive sessions (parts *A*, *B*, and *C*, respectively). The schedule is a fixed ratio 160. Reinforcements are marked by a resetting of the recording pen to the bottom of the record. Methamphetamine (2 mg.) was administered prior to part *B* (body weight—411 gm.).

The change in behavior at the beginning of part *C* could, therefore, have resulted from an earlier change in behavior due to the action of the drug.

As a base-line schedule for the study of drugs, a large fixed ratio is not completely satisfactory. With some subjects it is difficult to obtain a strained-ratio performance that is stable over extended experimental sessions. If the value of the ratio is moderate, some animals will not pause regularly, but if the value is increased, they will cease responding altogether.

A pause after reinforcement is obtained consistently with a schedule that is a special variation of the fixed ratio. This schedule has 3 tandem components consisting of an initial ratio followed by a minimum-rate contingency and a terminal ratio. The pigeon must first respond, for example, 18 times. After the 18th response the animal must allow a minimum of 2 seconds to elapse without a response and finally, following the 2-second pause, the animal must respond 4 times to receive reinforcement. These particular values are convenient, but not critical. The requirements are met in only 1 order. The

2-second pause, for example, is not effective prior to the 18th response. The first 2-second pause after the 18th response is effective, and the fourth response after the pause is reinforced. The animal is reinforced for a minimal number of responses if the 2-second pause occurs between the 18th and 19th responses. It should be noted that there are no changing exteroceptive stimuli associated with the various components of the schedule.

One advantage of this tandem schedule is that the ratio strain is readily produced. For a delay requirement of 2 seconds, relatively small values of the initial ratio will generate a pause after reinforcement. FIGURE 4 shows the effect of 0.3 mg. of methamphetamine injected intramuscularly 1 hour and 40 minutes before the start of part *B*. The values for the schedule are as follows: initial ratio, 48 responses; pause, 2 seconds; terminal ratio, 4 responses (in Ferster and Skinner's terminology of schedules[3] this would be called: tand FR 48 drl 2 FR4). Part *A* is the cumulative record for a complete experimental session on the day prior to drug administration. As before, the record is reset at each reinforcement. Even though the number of responses per reinforcement in part *A* is small, pauses clearly occur following reinforcement.

The effect of the methamphetamine injection is shown in part *B*. The pauses following reinforcement have virtually disappeared, but the local rate of responding has not been changed noticeably. The effect of the drug is similar to the effects of a comparably small dose on the strained-ratio performance produced by a fixed-ratio schedule.

Part *C* of FIGURE 4 is the response record for the day following drug administration. Although the pauses after reinforcement are again present, on the average they are shorter than in part *A*. This absence of complete recovery may be another instance in which the effect of a drug is prolonged beyond the actual persistence of the drug by the effect of the drug-influenced behavior on subsequent behavior.

FIGURE 5 shows the effect of a larger dose of methamphetamine on the tandem-ratio schedule described above. Parts *A*, *B*, and *C* are again records for 3 consecutive days. The effects of 1.7 mg. of methamphetamine, injected immediately before the record seen in part *B*, reproduce the effects of a large

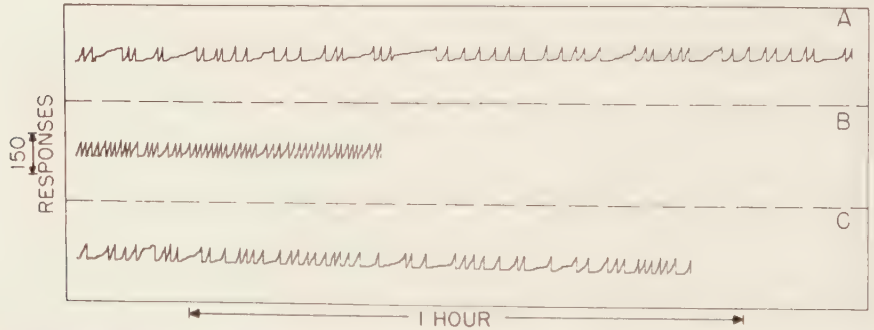

FIGURE 4. Complete cumulative response curves for 3 consecutive daily sessions (parts *A*, *B*, and *C*, respectively). The schedule is a Tandem FR (48) DRL (2 sec.) FR (4). Reinforcement is marked by a resetting of the recording pen to the bottom of the record. Methamphetamine (0.3 mg.) was administered prior to part *B* (body weight 418 gm.).

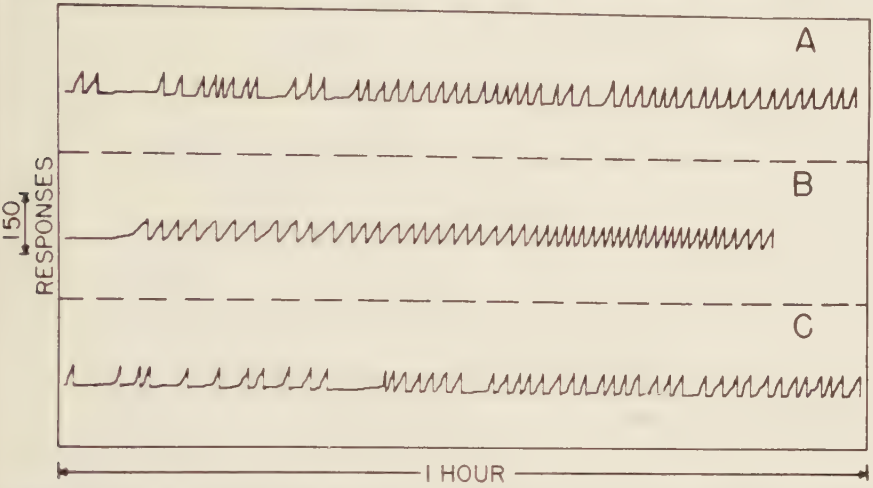

FIGURE 5. Complete cumulative response curves for 3 consecutive daily sessions (parts *A*, *B*, and *C*, respectively). The schedule is a Tandem FR 48 DRL 2 sec. FR 48. Reinforcement is marked by a resetting of the recording pen to the bottom of the record. Methamphetamine 1.7 mg. was administered prior to part *B* (body weight—410 gm.).

dose on the strained-ratio performance (FIGURE 3). As before, the pause after reinforcement has disappeared, and the local rates of responding have decreased. The rate also increases throughout the experimental session, as it did in FIGURE 3. An additional drug effect appears in the present record, however. Inspection of the individual segments between adjacent reinforcements in parts *A* and *C* reveals many instances in which responding is initially at a high rate and then declines to a lower rate. This deceleration in rate produces a negative curvature in the cumulative response curve. Since the animal is required to pause for a minimum of 2 seconds following at least 48 responses, the deceleration in rate prior to reinforcement seems understandable. Little evidence of negative curvature appears in the record for part *B*, however and, under the effect of the drug, the pigeon responds at a fairly constant rate between adjacent reinforcements.

The results for a different pigeon subjected to the same treatment are shown in FIGURE 6. Part *A* is the record for the day preceding drug administration, and part *B* is for the day of the administration of 1.7 mg. of methamphetamine injected immediately before the session. Unfortunately, owing to a breakdown of the recording equipment, the control record following part *B* was lost. As in the previous figure, the drug has again eliminated the pause following reinforcement, has lowered the rate of responding, and has abolished the negative curvature between adjacent reinforcements. A comparison of FIGURES 4, 5, and 6 with respect to the durations of the experimental sessions, however, shows a reversal. In FIGURE 6, part *B* is longer than the control record (part *A*), whereas in each of the 2 previous figures part *B* is the shortest. This reversal is highly instructive in showing that the changes in performance due to the drug depend upon the characteristics of the base line. Methamphetamine reduces the pause following reinforcement on ratio schedules.

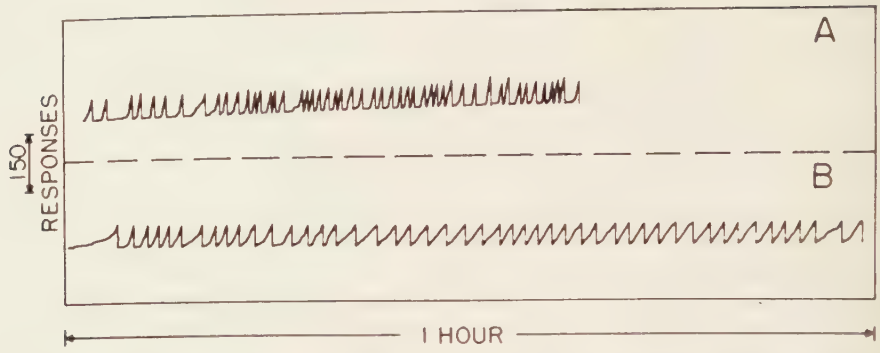

FIGURE 6. Complete cumulative response curves for 3 consecutive daily sessions (parts *A*, *B*, and *C*, respectively). The schedule is a Tandem FR (48) DRL (2 sec.) FR (4). Reinforcement is marked by a resetting of the recording pen to the bottom of the record. Methamphetamine (1.7 mg., was administered prior to part *B* (body weight—435 gm.).

This will be a major or minor effect of the drug, depending upon whether the base-line performance shows long or short pauses after reinforcement. In addition, the decrease in rate of responding following large doses of methamphetamine is most detectable when the rate in the base-line performance is high.

The tandem schedule used here generates a stable base-line performance that is more complex than that of the simple fixed ratio. The negative curvature in the control records of FIGURES 5 and 6 is evidence of this greater complexity. The behavior associated with this schedule can be more fully described, and the drug effects more precisely specified, when the behavior is subjected to a more detailed analysis.

FIGURE 7 shows the actual sequences of responses for 1 experimental session. A high-speed tape was used that fed continuously during a session when the schedule consisted of an initial ratio of 20, a minimum pause of 2 seconds, and a terminal ratio of 2. On this day the pigeon received 25 reinforcements. The line is displaced upward for the duration of each response and stays displaced

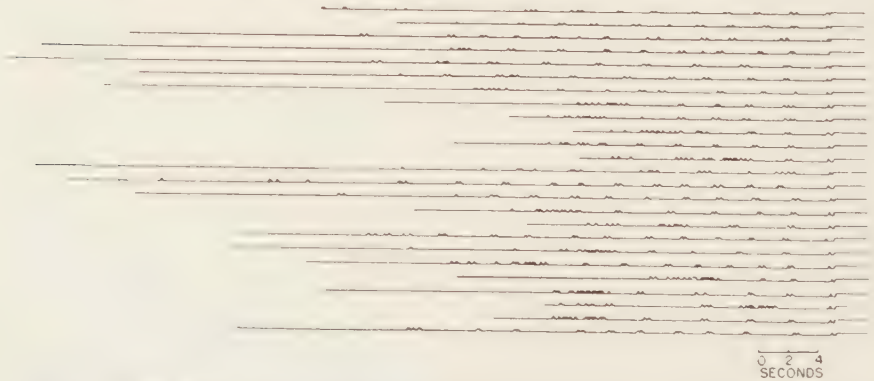

FIGURE 7. Complete response sequence for 1 experimental session. The schedule is a Tandem FR (20 DRL (2 sec.) FR (2). The recording pen is displaced upward for the duration of each response. The reinforced response and the reinforcements are marked as continuous displacements at the end of each line.

for the reinforced response. The tape has been cut and aligned on the reinforced response.

The characteristic most apparent on these tapes is the almost rigid patterning of the behavior. There is a strong tendency for long and short interresponse times to alternate. After emitting 2 responses at a high rate, the pigeon is likely to pause about 2 seconds before emitting the next response. In addition, this next response, itself, is very likely to be followed rapidly by another response. The patterning is a direct consequence of the arrangement of the reinforcement contingencies. The schedule of reinforcement requires that the penultimate interresponse time be of at least 2 seconds' duration. The group of 3 responses consisting of a long and a short interresponse time is reinforced when it occurs after the 20th response and the long interresponse time is greater than 2 seconds. Consequently, this chain of responses tends to occur repeatedly earlier in the sequence.

The regular cycling of long and short interresponse times indicates that the pigeon's behavior contains response chains that consist of the 2 different durations of interresponse times. After the first few reinforcements of each experimental session, an even more complex response chain develops. Following the seventh reinforcement in FIGURE 7 (counting from top to bottom) the pigeon tends to emit long series of responses at a high rate at the beginning of the sequence before showing the pattern of alternation seen in the earlier sequences. This new pattern shows that the presence of the initial ratio of 20 responses is exerting control over the behavior. The pigeon now meets the initial contingency in a more efficient manner than previously: that is, by emitting approximately 20 responses at a high rate and then alternating long and short interresponse times, the pigeon maximizes the frequency of reinforcement in time.

FIGURE 8 presents similar records for the same pigeon when the terminal ratio was 4 instead of 2. Of the 50 reinforced sequences comprising the experimental session only the first and last 10 have been reproduced. The patterning of interresponse times has changed appropriately. The pigeon now tends to emit cycles of 1 long (approximately 2 seconds) and about 3 short interresponse

FIGURE 8. Response sequence for 2 portions of 1 experimental session. The schedule is a Tandem FR (20) DRL (2 sec.) FR (2). The recording pen is displaced upward for the duration of each response. The reinforced response and the reinforcements are marked as continuous displacements at the end of each line.

times. Occasionally there are 2 or 4 short interresponse times instead of 3. The same shift that was observed in the previous figure during the day's session is detectable here. Toward the end of the session the pigeon begins each sequence with long runs of responses at a high rate.

These 2 figures show the effects that are produced by arranging tandem reinforcing contingencies within a single schedule. It is clear that the animal responds to contingencies that are remote from reinforcement, such as the 2-second pause and the fixed-ratio condition prior to the delay requirement. The effect of these remote contingencies is to produce a complex but highly consistent pattern of responding.

One way to summarize this patterning of responses is presented in FIGURE 9, which shows relative frequency distributions of interresponse times for the tandem schedule. The percentage of interresponse times within equal class intervals of approximately 0.1 second is shown for the terminal FR 2 and the terminal FR 4. In each case the delay requirement was 2 seconds. The distribution for the terminal FR 2 is for the same session as was shown in FIGURE 7. The distribution for the terminal FR 4 is for the same pigeon on a day when the session consisted of 25 reinforcements, thus making it comparable to the lower distribution. The schedule then consisted of an initial ratio of 18, a 2-second delay, and a terminal ratio of 4. The area under both of these distributions is slightly under 1.0 because a few interresponse times greater than 4 seconds occur and are not plotted.

Both distributions are distinctly bimodal. In both there is a peak at around

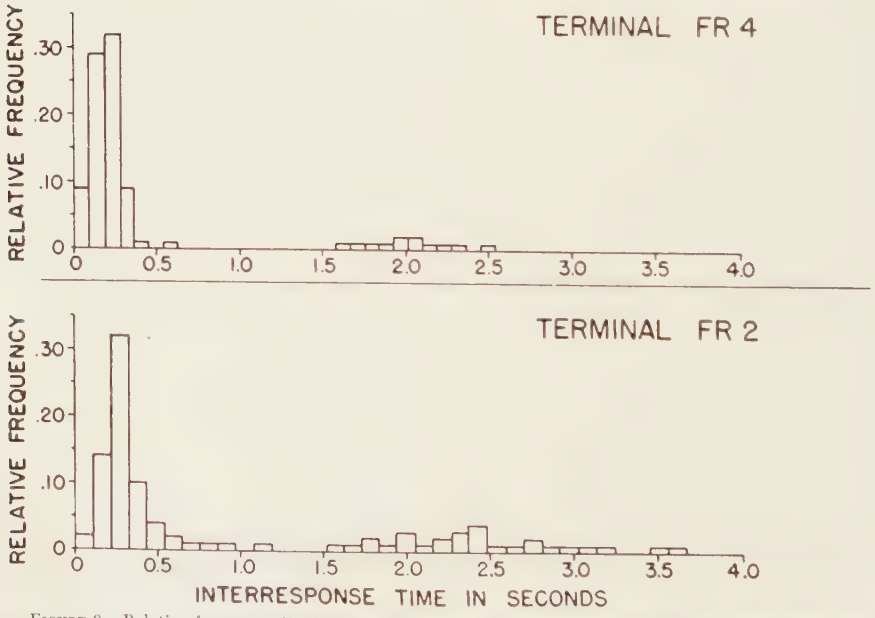

FIGURE 9. Relative frequency distributions of interresponse times in seconds for 2 complete experimental sessions. The schedules are a Tandem FR (20) DRL 2 sec. FR (2), and a Tandem FR (18) DRL (2 sec.) FR (4).

0.25 second that corresponds to the responding at high rates. In addition, a much smaller peak in the vicinity of 2.0 seconds occurs in each distribution. This peak is the result of the 2-second delay component of the schedule. The peak around 2 seconds is larger for the terminal FR-2 distribution than for the terminal FR-4 distribution. This difference is due simply to the difference between the response patterns generated by these 2 conditions. The cycles for the terminal FR 2 consist of alternations of long and short interresponse times. The cycles for the terminal FR 4 have 3 or 4 short interresponse times for each long one. It is obvious that the relative distributions of interresponse times will show a greater density of long interresponse times for the terminal FR 2 than for the terminal FR 4.

The characteristic patterns of interresponse times for the 2 values of terminal ratio are summarized in FIGURE 10. The graphs are for the same sessions shown in FIGURE 9. The value at *R* on the abscissa is the mean duration of the last interresponse time before reinforcement within a single session. Since

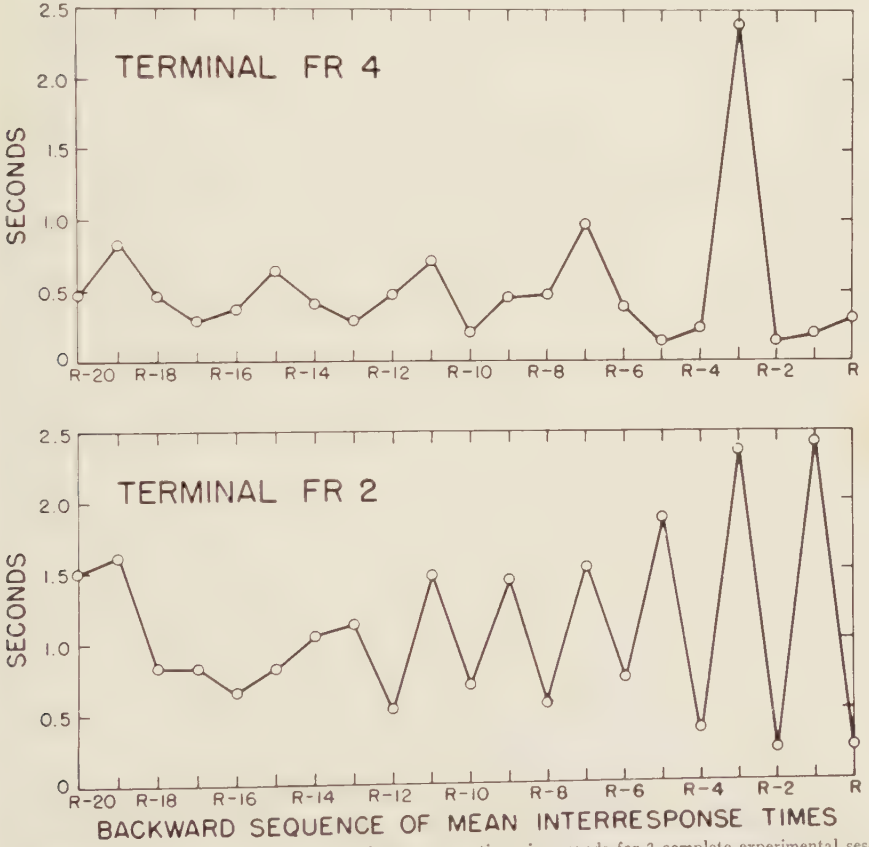

FIGURE 10. Backward sequence of mean interresponse times in seconds for 2 complete experimental sessions. The schedules are a Tandem FR 20 DRL 2 sec.) FR (2), and a Tandem FR (18) DRL (2 sec.) FR (4). See the text for an explanation of the abscissa.

a session comprised 25 reinforcements, the value is the mean of the 25 terminal interresponse times. Consequently, R can be considered as the mean reinforced interresponse time. The mean of the interresponse times directly preceding the reinforced interresponse times is plotted at $R - 1$. The value at $R - 1$ is, therefore, the mean time interval between the second and third response before reinforcement. The value at $R - 2$ is the mean time interval between the third and fourth response before reinforcement, and so on, down to $R - 20$, which is the mean time interval between the 21st and 22nd responses before reinforcement. Because the responses are counted in the order opposite to that in which they were emitted, these values are called a "backward sequence of mean interresponse times."

The measure used in FIGURE 10 depends not only upon the patterning of interresponse times within particular reinforcement sequences but also upon the phase relations among interresponse times in all of the sequences of a session. For example, with a terminal ratio of 2, the occurrence of 2 consecutive short interresponse times in a particular sequence, at $R - 4$ and $R - 5$, would mean that, even if there were strict alternation in long and short interresponse times, from $R - 6$ to $R - 20$, this sequence would be out of phase with any other sequence that had strict alternation in long and short interresponse times throughout.

The alternation of 1 long and 1 short interresponse time can be seen in the graph for the terminal FR 2. There are 6 clear cycles. The amplitudes of the cycles tend to get smaller for responses farther from reinforcement because deviations from strict alternation have a cumulative effect on the mean interresponse times. It should be noted that the value of $R - 1$ must be 2 seconds or greater, since a pause of at least this duration is required for the penultimate interresponse time before reinforcement. This value is slightly below 2.5 seconds, and it may be considered a measure of the precision of the pigeon's timing of the 2-second pause requirement.

The curve for the terminal FR 4 shows the patterning produced by this terminal ratio. The pigeon tends to alternate 1 long interresponse time with 3 short interresponse times. To some extent the cycling is evident throughout the curve. The difference between long and short interresponse times is smaller here than for the terminal FR 2. This, however, is not to be taken as an indication that long interresponse times were shorter for the terminal FR 4 than for the terminal FR 2. Inspection of the relative-frequency curves (FIGURE 9) shows that the pauses were of the same magnitude in both instances, but that they occurred more frequently when the terminal ratio was 2. The low amplitude of the cycles for the terminal FR 4 is due, rather, to the additive effect of deviation from strict grouping of interresponse times. As shown in FIGURE 8, the terminal FR 4 produces numerous deviations from the pattern of 1 long and 3 short interresponse times.

It was previously noted that when the terminal ratio is 2, the value at $R - 1$ cannot be less than 2 seconds. Since the mean value at $R - 1$ is obtained from 25 interresponse times longer than 2 seconds and 0 interresponse times shorter than 2 seconds, the value at $R - 1$ does not measure the consistency in the grouping of long and short interresponse times. Rather, it is a measure of

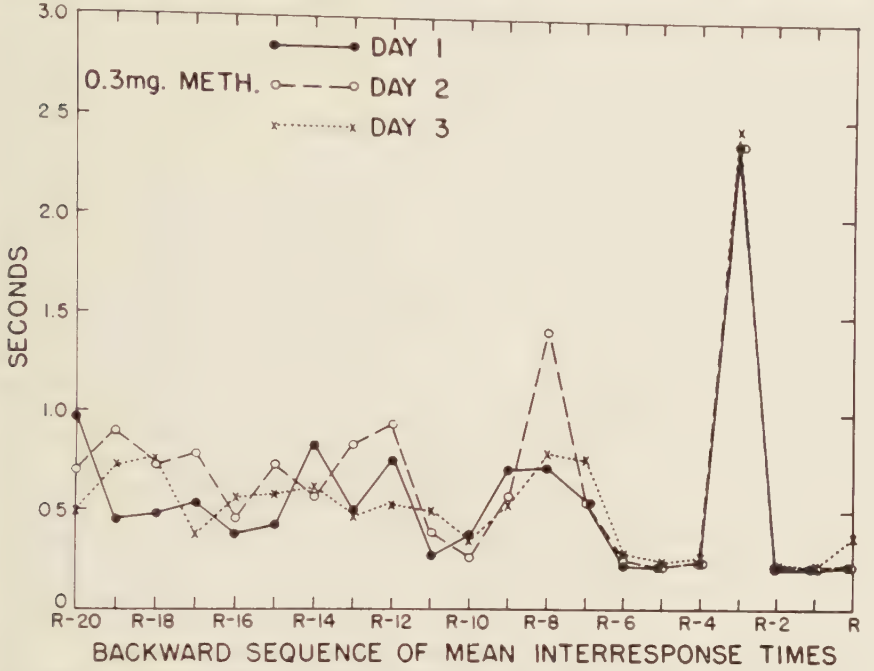

FIGURE 11. Backward sequence of mean interresponse times in seconds for 3 consecutive sessions. The schedule is a Tandem FR (18) DRL (2 sec.) FR (4). Methamphetamine (0.3 mg.) was administered 15 minutes before the start of Day 2 (body weight—412 gm.).

how well the pigeon meets the 2-second pause requirement. Correspondingly, the value at $R - 3$ is a measure of precision in timing when the terminal FR is 4. Comparing these 2 values in the 2 graphs will show that the precision in timing the 2-second pause requirement is the same in both instances. Even though the pause requirement is more remote from reinforcement when the terminal FR is 4, the mean interresponse time at $R - 3$ is as close to the 2-second minimum as the value at $R - 1$ when the terminal ratio is 2.

FIGURE 11 shows the change that took place in the backward sequence of mean interresponse times for a pigeon that was injected with 0.3 mg. of methamphetamine 15 minutes before the experimental session. The schedule consisted of an initial ratio of 18, a 2-second delay requirement, and a terminal ratio of 4. The figure shows the day of injection and the preceding and following control days. The value at $R - 3$ has not changed, which indicates that the timing of the 2-second delay has not become less precise on the day of injection. The only clear change in the backward sequences is seen at $R - 8$. Here the drug day shows a much higher peak than the control days. This increase was due to an increased number of long pauses at this point in the ratio. The methamphetamine strengthened the tendency for the animal to respond in the pattern of long and short interresponse times. On the cumulative record this change would have been seen as a decrease in negative curvature.

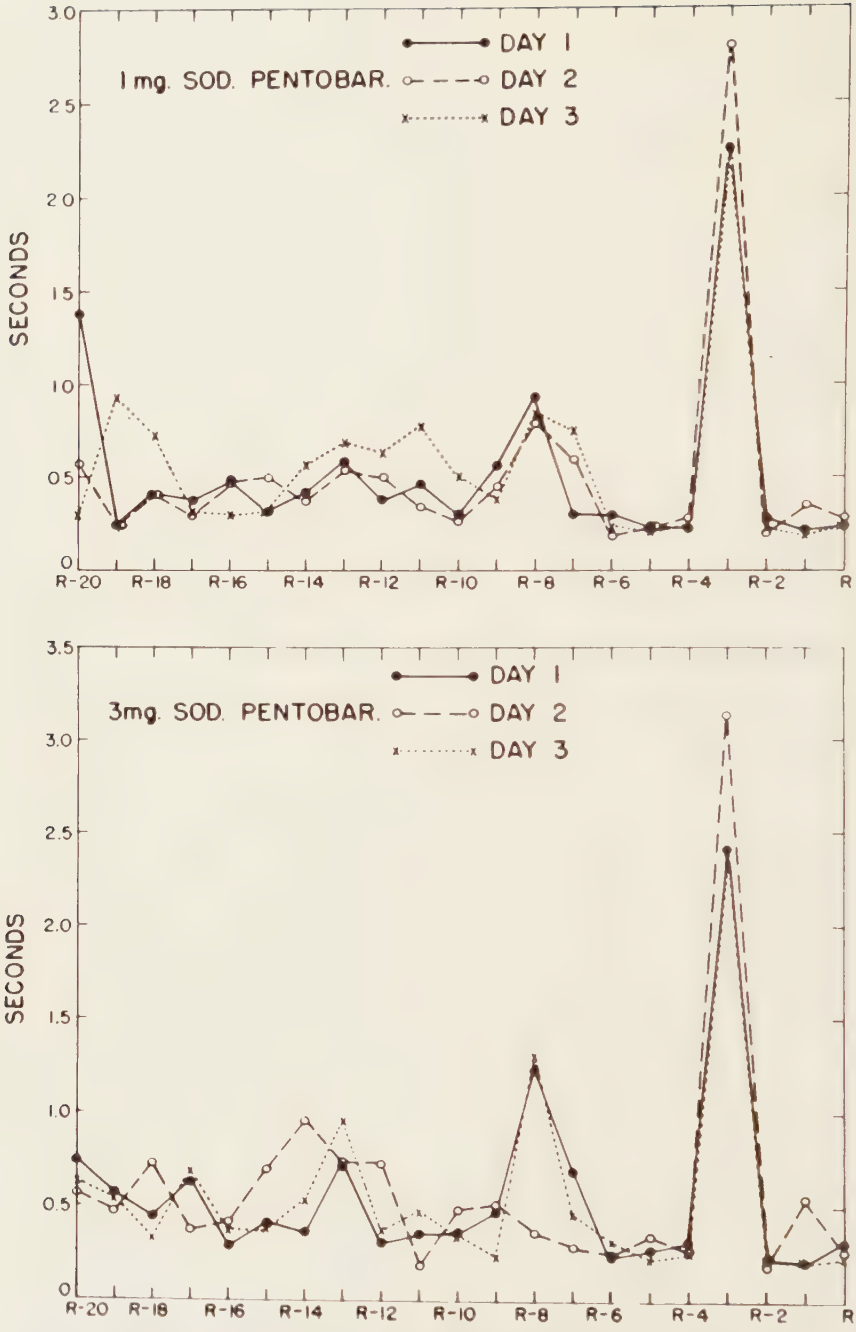

FIGURE 12. Upper and lower graphs both show backward sequences of mean interresponse times in seconds for 3 consecutive sessions. The schedule is a Tandem (FR) 18 DRL (2 sec.) FR (4). Upper graph: sodium pentobarbital (1 mg.) administered 15 minutes before the start of Day 2 (body weight—420 gm.). Lower graph: sodium pentobarbital (3 mg.) administered 15 minutes before the start of Day 2 (body weight—420 gm.).

This effect of methamphetamine on the backward sequence can be contrasted with the effect of sodium pentobarbital. FIGURE 12 shows the action of 2 different dosages of sodium pentobarbital administered 15 minutes before the session. As before, each drug day is accompanied by the preceding and following control days.

Unlike methamphetamine, sodium pentobarbital has an effect on $R - 3$: the average of the interresponse times that satisfied the delay requirement has increased due to the drug. This increase is greater for the 3-mg. dose than for the 1-mg. dose. Since $R - 3$ must be 2 seconds or above, the closer the value is to 2 seconds the more precisely the animal is timing the delay. The increase in this value that is caused by pentobarbital reflects, therefore, a loss of precision in the timing behavior.

The effect of pentobarbital on $R - 8$ is also clearly different from that of methamphetamine. The 3-mg. dose eliminated the peak at $R - 8$. There appeared, instead, a much reduced peak at $R - 9$ and $R - 10$. This was not a change in the durations of interresponse times as much as a change in the patterning of interresponse times. Instead of alternating 3 or 4 short interresponse times and 1 long interresponse time, the pigeon tended to have longer runs of short interresponse times. The 1-mg. dose, however, did not change the patterning from that of the control days, although it did affect the precision in timing the delay requirement.

The drug effects on the backward sequences have been small ones. In all the examples shown, the drugs have had so minor an effect on behavior that neither the durations of the sessions, the rates of responding, nor the total number of responses per reinforcement have been substantially altered. The presence of several different characteristics of the base-line behavior made a finer analysis of the drug effects possible. Both the timing and the patterning of behavior proved to be clearly sensitive to the drugs, even when the grosser aspects of the behavior remained essentially unaffected.

Summary

Characteristics of behavior that are differentially sensitive to drugs can be generated by scheduling different contingencies of reinforcement. Complex behavior patterns, where there are no exteroceptive stimuli associated with the reinforcing contingencies, have been found to be especially valuable base lines for studying the effects of drugs on learned behavior.

Acknowledgment

We acknowledge the cooperation and helpful advice we received from C. B. Ferster, P. B. Dews, and B. F. Skinner in conducting these experiments.

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EFFECTS OF DRUGS ON MOTIVATION: THE VALUE OF USING A VARIETY OF MEASURES*

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In studying the effects of drugs on motivation it is desirable to use a number of techniques that are as diverse as possible in order to avoid misleading generalizations from effects that are specific to the particular indicator used. Some of the preceding papers by students of Fred Skinner have shown unusual ingenuity in using the same instrumental response (pressing a lever or pecking at a panel) in a variety of different testing situations. There are definite advantages to this procedure of using the same response in a variety of different tests, and the tests that have been described in the other papers have many additional excellent attributes. For example, bar pressing reinforced on a variable-interval schedule may be maintained at a constant rate for a considerable time with relatively minor consumption of food (and satiation of drive), so that the course of drug effects may be followed economically throughout fairly long periods. Nevertheless, I believe it is also desirable to have tests that are still more diverse in that they do not depend on the same response and, hence, can insure us against being misled by effects that are specific to that response. In this connection the standardization of naturalistic observation so interestingly presented in the first paper (de Beer and Norton, 1956) should prove fruitful.

Since I am advocating the use of a diversity of behavioral measures, it will be appropriate to illustrate the application of a variety of techniques to a number of different problems. It will be efficient to begin with a brief reference to the development and use of certain measuring techniques in nonpharmacological studies of "hunger" and "thirst" followed by a description of the application of the same measures to a study of the effects of amphetamine.

Next I shall describe some techniques for studying conflict behavior that were used in a theoretical and experimental analysis of some of the social effects of alcohol. I shall also mention an attempt to develop a new behavioral measure of fear-motivated behavior and to use this measure to compare the effects of reserpine on a response motivated by fear with its effects on the same response motivated by hunger.

I shall point to the possibility of increasing our knowledge of the central effects of drugs by combining the techniques of using implanted electrodes for electrical stimulation of the brain of the unanesthetized animal with the behavioral techniques for studying avoidance and also reward learning. I shall conclude with the importance of basic research in the development of a science of psychopharmacology (or, if you prefer, behavioral pharmacology) that eventually may provide a rational basis for practical applications to mental hygiene in the same way that organic chemistry provides a basis for the synthesis of new compounds.

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Some Studies of "Hunger" and "Thirst"

One might think that the amount of food consumed is the best measure of the motivating effect of food deprivation. If one is interested solely in problems of energy exchange and weight regulation, food consumption is a highly relevant measure. If one pursues the broader problems of motivation, however, a paradox develops. In albino rats, the amount of food consumed in a single session before satiation increases as a function of increasing deprivation to a period of approximately 1 day, after which further increases in deprivation fail to produce additional increases and may even decrease the amount of food consumed. As Heron and Skinner (1937) and others have shown, however, the rate at which animals will work for food at a bar-pressing task, reinforced on a variable-interval schedule, will continue to increase during 4 or 5 days of food deprivation, or until shortly before the animal's death.

The consumption response and the rate of bar pressing produce contradictory results. What would other measures show? In an attempt to answer this question, Mrs. M. L. Kessen and I (Miller, 1955) have devised a new technique that has proved to be generally useful. A series of bottle caps are countersunk on the periphery of a metal disc that is driven by a slipping clutch and escapement mechanism. The bottle caps appear immediately below an opening in the floor of a small cage that is arranged so that the rat can reach only 1 cap at a time. After a hungry rat has learned to drink a few drops of milk from each bottle cap as soon as it appears, it is presented at 30-second intervals with a series of 10 bottle caps, each cap containing 3 drops of milk, and each solution being adulterated with progressively increasing amounts of quinine hydrochloride ranging from concentrations of 0, 0.004 per cent, 0.008 per cent, to 1 per cent.* For each cup that he cleans up, the rat receives 2 points; for each one started without finishing, 1 point; and for cups not touched, zero. The cumulative score has been found to be a sensitive and reliable measure of hunger. Perhaps this measure could be further improved by using an electronic relay to measure drinking from a device such as that developed by Stellar and Hill (1952).

FIGURE 1 summarizes the results of a study comparing the quinine score with other measures of "hunger." Each rat was tested in a balanced order after each of the periods of deprivation listed on the abscissa. Tests were separated by 3-day periods of *ad libitum* feeding. Each measure is plotted as a standard score derived from the average within-test-condition variability on the last 3 deprivation intervals, which are those common to all measures. It can be seen that with increased hours of deprivation the amount of milk consumed increases (from the presumed score of little or no drinking, which was not taken and is not represented) and then levels off. The rate of bar pressing, reinforced on a variable-interval schedule, increases progressively throughout the intervals tested. Our new quinine measure agrees quite well with the bar-pressing measure, forming a slender, 2-to-1 majority of behavioral measures, with the more obvious measure of the amount of food consumed in the minority. The physiological measure of stomach contractions, recorded

* Mrs. Kessen actually used a slightly different series of solutions of quinine sulphate. We are describing the improved procedure used in subsequent experiments.

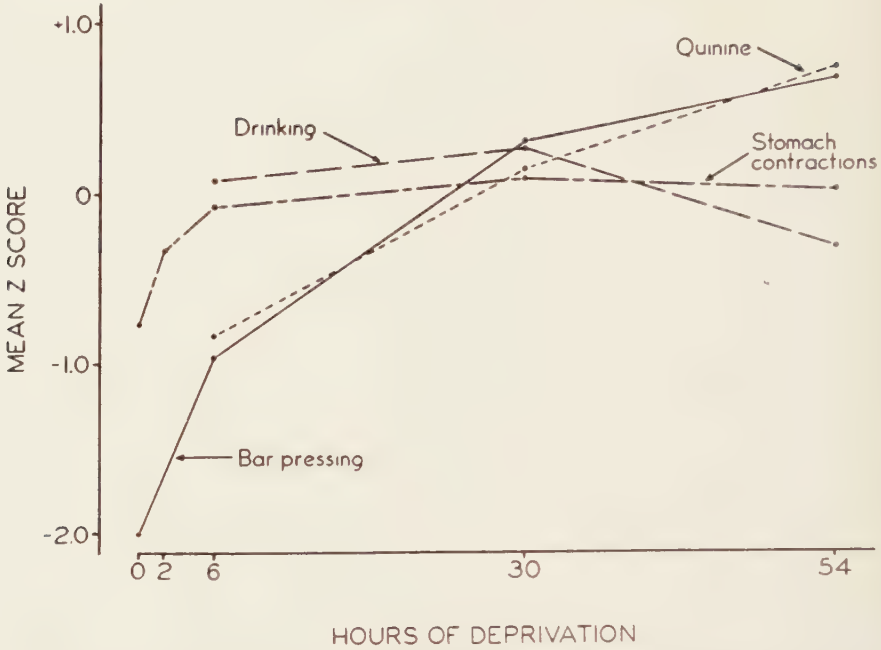

FIGURE 1. Comparison of 4 measures of "hunger": (1) the volume of enriched milk drunk by rats before satiation; (2) the amount of quinine required to stop drinking; (3) the rate of bar pressing reinforced by food on a variable-interval schedule; and (4) the sum of excursions of the record of stomach contractions measured from a balloon permanently implanted on the end of a plastic fistula.

from a small balloon permanently implanted in the stomach on the end of a plastic fistula, does not appear to be very sensitive and seems to level off somewhat as the consumption response does.

In any event it is perfectly clear that, in the higher ranges, the consumption response can yield different results from those of the bar-pressing and quinine measures. Presumably this is due to the fact that the volume of the stomach, or the amount of food that the deprived animal can handle, reaches an upper limit long before the general effects of emaciation affect the other 2 measures.

Let us turn now to the results of similar measures in a study of "thirst" by one of my students, Martin Choy (1956). The experimental treatment used was the administration of 5cc. of a 2-molar saline solution via stomach tube to albino rats that had been on *ad libitum* food and water. A 9-minute bar-pressing test reinforced by water on a variable-interval schedule was followed immediately by a measure of the volume of water consumed within 15 minutes, which seemed to be a sufficient time interval for satiation. In a balanced Latin-square design, each animal was tested on different days after intervals of 15 minutes, 1 hour, 3 hours, and 6 hours following treatment. In an immediately subsequent experiment on the same rats, a quinine-water test, analogous to the quinine-milk test already described for hunger, was also used.

The results of all 3 tests are presented in FIGURE 2. We can see that if Choy

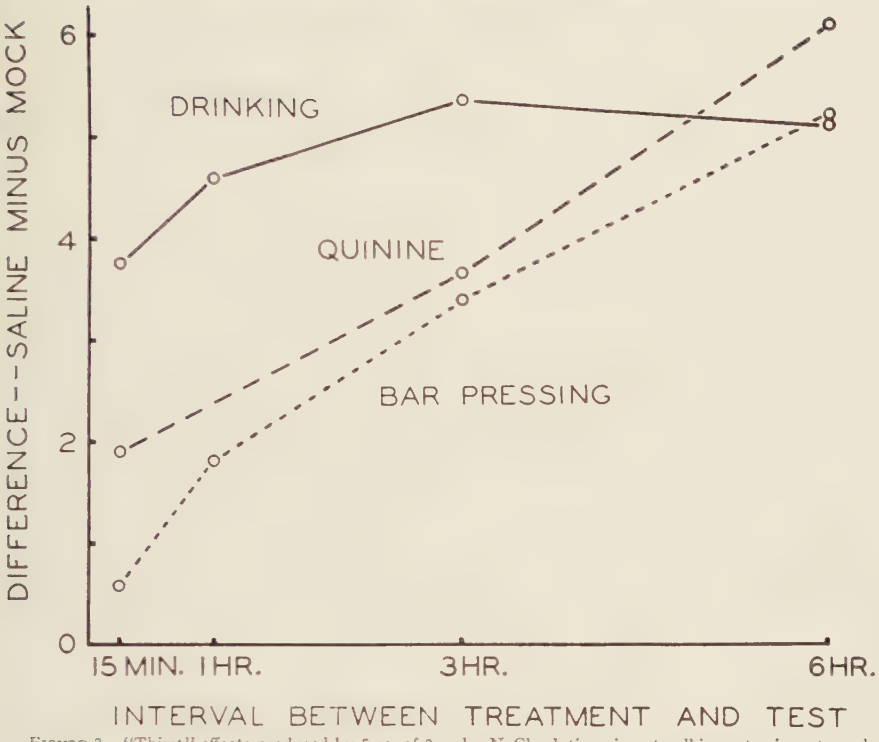

FIGURE 2. "Thirst" effects produced by 5 cc. of 2-molar NaCl solution given to albino rats via a stomach tube. The units on the ordinate are the amount by which the experimental test exceeded the control test given at the same time. To yield differences on various tests, these units should be multiplied as follows: ×1 for the quinine score described in the text; ×2 for cc. of water drunk to satiation; ×10 for the number of bar presses during 9 minutes.

had administered only the single test of bar pressing he would have concluded that the 2-molar saline solution produced little if any effect within 15 minutes, since the difference at this time is small and does not approach statistical reliability ($P > 0.20$). This conclusion would be false, since the other measures show large and reliable differences on the 15-minute test. Perhaps the bar-pressing test is insensitive at this point of the scale, or it may be depressed more than the other 2 tests by distracting stimuli from the recent stomach load of 2-molar saline. The latter hypothesis could be checked by comparing the aftereffects of other distracting stimuli, such as mild electric shocks, on the 3 measures.

Looking now at the latter part of the curves, it is furthermore apparent that if Choy had used only the test of amount for water consumed, he would have concluded that the effect reaches its maximum within 3 hours, since that measure levels off after the 3-hour test. This conclusion would be false also, since the other 2 measures show large and reliable rises between the 3- and 6-hour tests. Perhaps the amount consumed reaches a ceiling determined by the volume of the stomach. This hypothesis could be tested by studying the effects of making a fistula in the esophagus, then aspirating part of the

water via a stomach fistula, or reducing the volume of the stomach by inflating a little rubber balloon on the end of a permanently implanted plastic fistula into the stomach.

To summarize, in this particular situation the consumption response is sensitive only at the shorter intervals, the bar-pressing test is sensitive only at the longer intervals, and the quinine test is reasonably sensitive throughout the range.

In another experiment in the same series, Choy used the convenient procedure of administering the 3 tests in immediate succession. A 9-minute sample of bar pressing was followed by a 4½-minute quinine test and then a 15-minute test of the amount of water consumed. The 2 treatments compared are: (1) the control treatment of a mock injection to animals that had been on *ad libitum* food and water, and (2) the experimental treatment of allowing animals that had had water available but had been deprived of food for 23 hours, to eat dry food without water for 15 minutes and then giving them 5 cc. of 2-molar saline by stomach tube. FIGURE 3 shows that this treatment produced a marked and reliable increase in the amount of water consumed, some increase in the quinine score, but a large and reliable decrease in the rate of bar pressing.

To recapitulate, we see that the consumption response and the bar-pressing response can yield different, and even contradictory results. To date, the

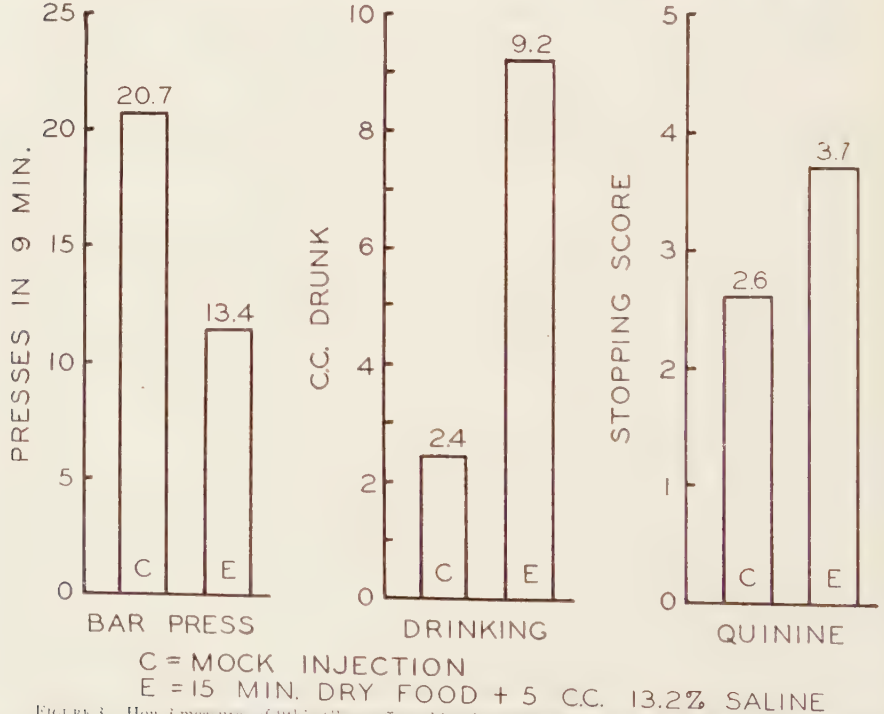

FIGURE 3. How 3 measures of "thirst" are affected by the experimental procedure of feeding dry food without water to hungry rats and then administering 5 cc. of 13.2 per cent saline via stomach tube.

quinine test has always occupied an intermediate position between these 2, agreeing with either one or the other but never finding itself in the minority of being lined up against the other 2 tests.

We have presented these examples, in which the consumption and bar-pressing measures disagree, in order to make the point that it is possible for them to yield different results. In many other studies (summarized by Miller, 1955), however, these 2 measures show exactly the same pattern of results.

Experiments on Amphetamine

Having approached our topic gradually, via the administration of a strong solution of sodium chloride, let us turn now to a study using a genuine drug, racemic amphetamine sulphate. An early study on only 4 rats by Wentink (1938) indicates that this drug will increase the rate at which animals will work for food when bar pressing is reinforced on a variable-interval schedule, but will decrease the amount of food consumed immediately afterward. What will the effect of this drug be on our quinine score?

In the first of a series of experiments performed with the assistance of Judith A. Berman, 11 male albino Sprague Dawley rats, ranging from 326 to 466 gm., were given subcutaneous injections (0.5 cc. per 100 gm. of body weight) of: (1) either a control solution of isotonic saline, or (2) a solution of 0.6 mg. of amphetamine sulphate per cc. of isotonic saline (that is, 3 mg. per kilo.). The animals were tested when they were 23 hours hungry and rewarded with small pellets of food. Three tests were employed: (1) 9 minutes of bar pressing with a reinforcement for the very first response and for the first response after 6 minutes;* (2) a quinine-milk test similar to the one already described and lasting $4\frac{1}{2}$ minutes; and (3) 1 hour of eating a mash of equal weights of laboratory chow and water, with additional water available. The amount of food consumed was measured at the end of both a half hour and 1 hour. Since the results were substantially the same, those of the full hour were used. The tests were administered in immediate succession beginning 20 minutes after injection. In every instance the eating test necessarily was always last, but the bar-pressing test was administered first for half the animals and the quinine test first for the other half. Half of the animals were tested after saline and the remainder after amphetamine. Two days later the tests were repeated with these conditions reversed so that each animal served as his own control.

The results are presented in FIGURE 4. It can be seen that the drug produced a reliable decrease in all 3 tests, and that the quinine test appeared to yield the most reliable difference. Furthermore, a similar experiment on a different group given a somewhat smaller dose of amphetamine (2.1 mg. per kg.) yielded the same decreases in the quinine and consumption tests, but variable and unreliable effects on bar pressing.

Since the effects of the drug on the bar-pressing measure in the first experiment were the reverse of those reported by Wentink (1938) for a somewhat similar schedule and were also opposed to those reported by Skinner and Heron (1937) for rats that had been extinguished by nonrewarded trials, we decided

* The animals had previously been thoroughly trained on a variable-interval schedule averaging 2 reinforcements every 3 minutes.

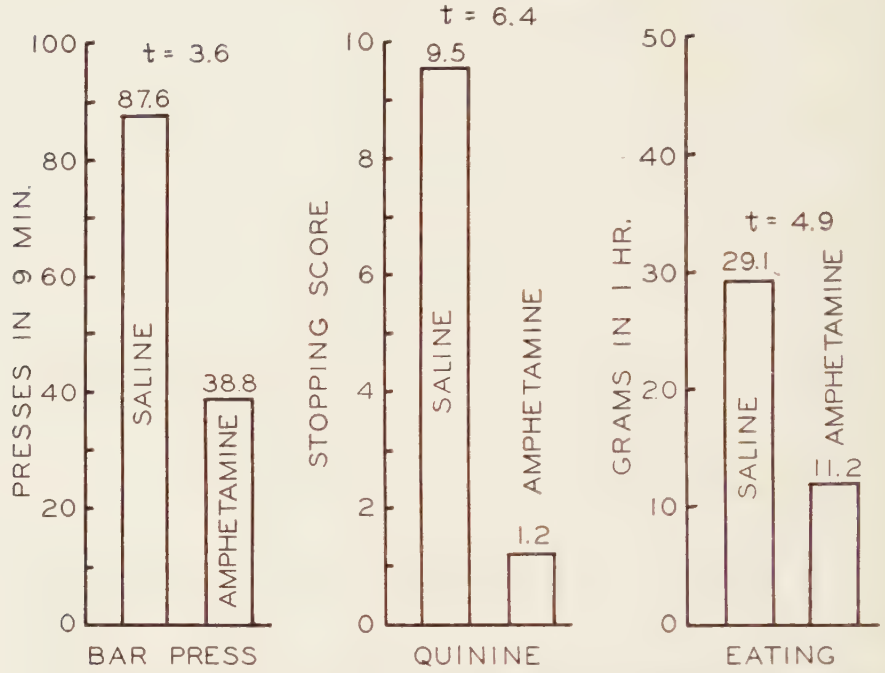

FIGURE 4. Effect of amphetamine (3 mg. per kg.) on 3 measures of "hunger" administered to food-deprived rats. The bar pressing is reinforced on a variable-interval schedule.

to repeat this latter experiment. Since the procedure involved experimental extinction, injection of the drug, and then a continuation of extinction for an additional hour, limitations on our schedule made it necessary to omit the quinine test. Each of 6 rats was given in succession: (1) 15 minutes of nonreinforced bar pressing; (2) a control injection of isotonic saline or an experimental injection of 2.1 mg. of amphetamine per kg.; (3) 1 hour of nonreinforced bar pressing; and (4) 1 hour of a mixture of equal weights of laboratory chow and water, with water available. After a 2-day interval the test was repeated with the control and experimental injections reversed.

The result was that the control rate of 75 was increased by the amphetamine to a rate of 192 nonreinforced bar presses during the hour ($t = 2.0$). The amount of wet mash consumed was only slightly and unreliably decreased.

Since an analysis of the bar-pressing scores in the preceding experiment by 3-minute intervals showed that the maximum effect seemed to be achieved after 9 minutes, we were able to add the quinine test in another experiment on 12 rats with the following design: (1) 15 minutes of nonreinforced bar pressing; (2) a control injection of isotonic saline or an experimental one of 2.1 mg. of amphetamine per kg.; (3) a 9-minute rest in the home cage; (4) a 4 $\frac{1}{2}$-minute quinine test; (5) 15 minutes of nonreinforced bar pressing; and (6) 1-hour access to the wet-mash mixture with water available. Half of the animals were always given the quinine test first and the bar-pressing test second. This sequence was reversed for the other half. Half of each of these groups was

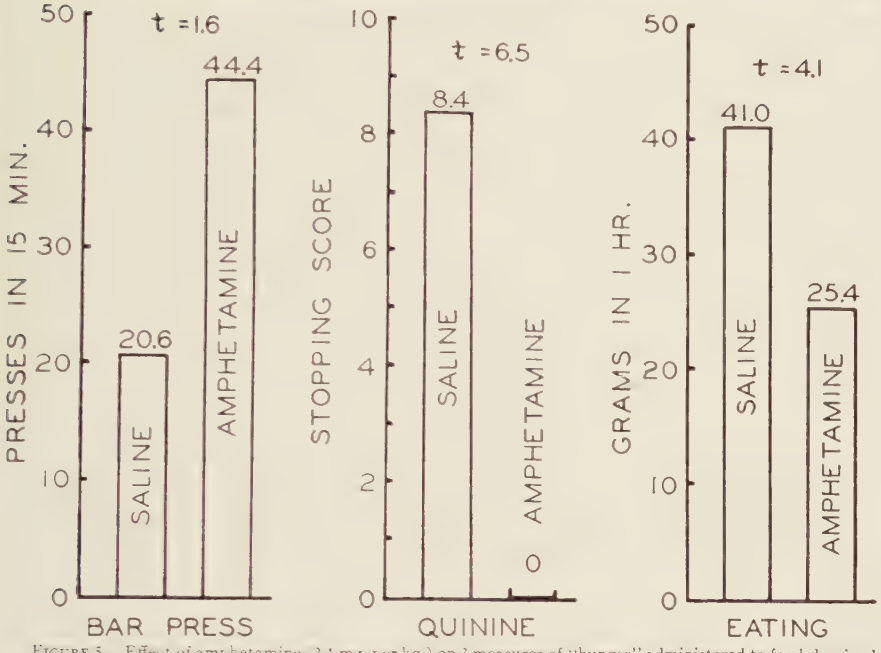

FIGURE 5. Effect of amphetamine (2.1 mg. per kg.) on 3 measures of "hunger" administered to food-deprived rats. The bar pressing has been previously experimentally extinguished and continues to be nonreinforced.

given the experimental treatment first and the control treatment 2 days later, the sequence again being reversed for the other half.

The results are presented in FIGURE 5. Again the amphetamine produced an increase in the rate of nonreinforced bar pressing. Although the results were so variable that this increase was reliable only at the 14-per cent level, when combined with those of the previous experiment they yield convincing evidence that, on the average, the effect of this dose of amphetamine is to increase the rate of nonreinforced bar pressing. At the same time, its effect is to produce large and highly reliable decreases in the quinine score and the amount of food consumed.

Throughout all of the preceding experiments the effects of amphetamine have been always to decrease the scores on the quinine and consumption tests. This drug seems to have variable effects on the bar-pressing measure, however. At the higher dose (3 mg. per kg.) it produces a reliable decrease in the high rate maintained by a variable-interval schedule. At a 30-per cent lower dose (2.1 mg. per kg.) its effects on this same high rate are variable and unreliable, and at this same lower dose it produces a sizable and fairly reliable increase in the low rate obtained during experimental extinction.

Some of our earliest studies (Miller and Miles, 1935 and 1936) showed that the stimulating effects of caffeine and the depressing effects of alcohol, respectively, were both greatly increased when the animal was slowed down by either experimental extinction or satiation. The present experiments may involve a factor of this kind along with a further complication. Perhaps we are dealing

with dual effects, such as a decrease in hunger but an increase in motor stimulation, that are differentially affected by our experimental operations so that the balance is thrown in favor of a different effect when the test is given with a different schedule. Even if these tentative hypotheses are wrong, the practical implications of our data are clear. We must be cautious about generalizing from the results of a single type of test.

The results of the foregoing experiments suggest that amphetamine reduces hunger but has a stimulating motor side effect that may, under certain circumstances, produce an increase in the rate of bar pressing. One might go on, however, to ask a further question: Does the drug produce a genuine reduction in hunger or does it induce some other drive, such as nausea, that conflicts with the hunger? My own subjective experience suggests the latter. This question is not only of theoretical but also of practical importance. We should expect a genuine reduction in hunger to serve as a reward, but the induction of indigestion to serve as a punishment. In fact, effects of the latter kind caused me to discontinue the use of an appetite-reducing drug.

The difference between these 2 effects suggests an experimental procedure for discriminating between them. Since this procedure has not yet been used on drugs, we shall have to illustrate it in another context. In other studies (Miller, 1955) I have found that the injection of milk directly into the stomachs of hungry rats via a permanently implanted plastic fistula will reduce the rate at which the animal will work for food. A similar result is produced by inflating a balloon on the end of such a fistula. That these apparently similar effects are actually qualitatively different is shown by the fact that hungry rats trained in a simple T maze will learn to go to the side where their stomachs are distended by milk, but will learn to avoid the side where their stomachs are distended by a balloon. It seems probable that a similar test could be used to differentiate between any rewarding or punishing effects of certain fast-acting drugs, provided that they could be administered by a relatively painless method.

Contradictory Results May Ultimately Lead to Better General Principles

We should not be discouraged by the fact that different measures can yield different results. Science looks for general principles, but its history often goes through a series of cycles somewhat as follows:

(1) Where there are relatively few facts it seems easy to account for them by a few simple generalizations. For example, in the absence of exact observations it seems obvious that heavenly bodies circle around the earth.

(2) As more facts are gathered, more exceptions to the general principles arise, and everything seems horribly complex. Any simple explanation seems completely out of the question. The late stages of the Ptolemaic system of cycles and epicycles continues the example from astronomy.

(3) A radical reorganization may occur either dramatically or piecemeal. It is found that a wide range of hitherto baffling phenomena can be subsumed under a few simple laws. An example is the change to a heliocentric system and the formulation of Newton's laws of motion.

(4) The theoretical advance leads to the collection of new facts that bring

out more exceptions, and the cycle is repeated, but the gains of the first cycle are not lost.

Our drug studies are probably in the process of shifting from the first to the second stage of such a cycle. As we begin to study the effects of a variety of drugs on a number of different behavioral measures, exceptions and complexities emerge. We are forced to re-examine and perhaps abandon common-sense categories of generalization according to convenient words existing in the English language. As new and more comprehensive patterns of results become available, however, new and more precise generalizations may emerge. We may be able to "carve nature better to the joint" and achieve the simplicity of a much more exact and powerful science.

Measures of "Fear" and "Conflict": Effect of Alcohol

Now I should like to summarize briefly a type of theoretical and empirical analysis that, for the moment, is yielding a more optimistic picture. Perhaps it is stage 3 in the cycle just described. Perhaps it is only stage 1.

The social effects of alcohol have been puzzling to me for a long time. Alcohol is supposedly a depressant, but the increase in the noise level during a cocktail party obviously does not indicate depression. One attempt to resolve this paradox is to assume that the higher functions are depressed first, releasing the lower ones. It is not clear to me, however, that the functions involved in standing shyly and mutely in a corner are necessarily always higher than those of becoming the life of the party after several drinks. Furthermore, alcohol has a puzzling variety of effects on different people, making some bellicose, others lacrymose, some amorous, and others loquacious.

The first experimental step toward resolving this dilemma was taken by Masserman and Yum (1946). These investigators demonstrated that alcohol can relieve the so-called experimental neurosis of cats who had been taught a complex series of manipulations to get food and then were frightened at the goal. In our laboratory, however, Conger (1951) believed that the complex series of manipulations and the so-called experimental neurosis were unnecessary. He reduced the matter to a simple approach-avoidance conflict by first training rats to run down a short alley to get food and then checking them with electric shocks at the goal, with the result that they just barely stopped eating there. After a control injection of isotonic saline the animals still refused to eat. After a moderate injection of alcohol they resumed running to the goal and eating.

These results could have been produced by either one or both of 2 factors: (1) an increase in approach motivated by hunger, or (2) a decrease in avoidance motivated by fear. To test for these factors, Conger had his animals wear harnesses, and he trained 1 group to approach a place where they received food and another group to avoid a place where they received shock. Then he measured the strength of each tendency by a technique that had been previously used in our laboratory (Brown, 1942)—measuring the strength with which the animals pull against a temporary restraint (FIGURE 6). He found that the pull of the hungry animals was the same under control and under alcohol injections, but that the pull of the avoidance animals was markedly

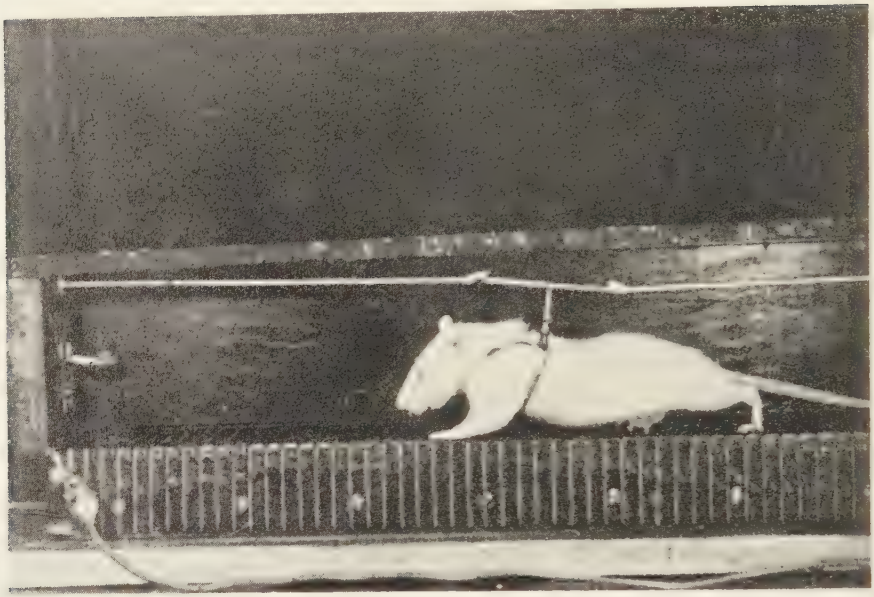

FIGURE 6. Strength-of-pull technique. The rat is temporarily restrained when approaching food (or avoiding electric shock), and the force with which he pulls against a calibrated spring is recorded

reduced by alcohol. Since the avoidance was stronger than the approach on the control test and weaker than the approach after the alcohol (a reversal in direction of difference), the results could not possibly be explained as an artifact of different-sized units of measurement at different points of the scale.

Finally, Conger used a third technique. He trained hungry animals to run down an alley for food. Then he gave them a series of trials, sometimes drunk and sometimes sober. One group was given electric shocks if they touched the food when sober, but were not shocked if they ate the food when drunk. The other group was trained under the opposite conditions of no shock at the food when sober, but shock when drunk. Both groups learned the discrimination but, as would be expected, the group that would be favored by a fear-reducing effect of alcohol—learning to be bold when drunk and cautious when sober—learned much more rapidly than the group that had to overcome this fear-reducing effect and learn to be careful when drunk and bold when sober. Thus the hypothesis was confirmed by results from a different technique.

If we think of alcohol as reducing the relative strength of the avoidance tendencies, or of social inhibitions motivated by fear, some of the paradoxical effects are easier to understand. It is not that becoming the life of the party is a less complex or lower function than standing mutely in a corner, but rather that the lively social responses have been inhibited by conflict with the shy, mute behavior motivated by fear. As the balance of the conflict is shifted, the inhibited activities emerge, and the decibel level of the party is raised. Furthermore, the specific type of activity to emerge will depend upon the

type of activity that was inhibited by conflict. A person with strong hostile tendencies that are barely inhibited will become aggressive, and one with inhibited strong sexual tendencies will become amorous. Finally, the effects of alcohol will be expected to vary with the relative strength of the tendencies in conflict. As Dollard and Miller (1950) have explained in more detail, a person whose conflicts are relatively evenly balanced will be expected to show a considerable effect and, if the consequences of his actions are not socially punished, to experience considerable relief. The alcohol only weakens somewhat the avoidance tendencies motivated by fear, however. If, accordingly, these tendencies were extremely strong originally, the person may remain inhibited after inebriation. In fact, he may be shifted from the comfortable position of not being tempted at all to the uncomfortable one of being released enough to be strongly tempted without being able to achieve his goal. The conflict may be intensified rather than relieved. From this analysis we begin to see why the same drug, under different conditions, may be expected to produce quite different effects.

Although I believe that the foregoing analysis contains large elements of truth, we may not yet have achieved quite the correct picture. I have found it difficult to repeat Conger's strength-of-pull experiment when the age of the habits involved was controlled. Perhaps recency, or sequence of learning, is an important factor. I have also found it difficult to repeat the results of Masserman and Yum (1946) on addiction in a modified situation, which involved only fear but which, according to my analysis, should have yielded similar results. This difficulty may represent a weakness in my theoretical analysis,* or it may merely be the result of technical difficulties that made it hard to realize appropriate test conditions.

Measures of Fear: Effects of Reserpine

Another of my students, Mitchell M. Berkun, has attempted to devise a different way of measuring hunger-motivated and fear-motivated behavior under strictly comparable conditions. Berkun locked rats in a distinctive box and gave them electric shocks at various intervals to establish fear of the box. Then on trials without further electric shocks they were trained to escape from the fear-evoking box in the following stages: (1) to run out into a "safe" goal box as soon as the door was dropped; (2) to press a bar that immediately dropped the door to the escape goal box; and (3) to press the bar that was set to drop the door in a variable-interval schedule. Hungry animals were trained in a similar series of stages to run out of the box to get food. The end result was 2 groups of animals each pressing the same bar on the same variable-interval schedule to get from 1 box to the other. One group was working to get out of the frightening box, and the other was working to get into the box with food. When the rats in the former group seemed to be extinguishing their fear they were given refresher shocks with the door locked and no bar present.

* For example, it is possible that conflict is itself a source of motivation that adds to that of the hunger and fear involved in the conflict. This conflict-induced motivation could be either especiallly strong and disruptive or especially susceptible to reduction by alcohol. Therefore conflict (in addition to fear) might be necessary in order to produce addiction.

In one unpublished exploratory experiment, Berkun used this technique to compare the effects of various doses of reserpine (0.25 mg., 1 mg., and 2 mg. per kg. per day, respectively) on the performance of his 2 groups.* Over a period of days, the drug produced a definite decrease in the performance of both groups (compared with saline-injection controls) as measured both by an increased time required for the first bar press and by a decreased rate of bar pressing. The larger doses produced greater effects (the largest dose eventually killing some of the animals), but there was no obvious difference in the effects of reserpine on the fear-motivated and hunger-motivated rats. This result is similar to that reported for a somewhat analogous comparison on monkeys by Weiskrantz and Wilson (1955).

Combining Central Stimulation with Behavioral Techniques

As the final measure, let us note the combination of the following 2 types of techniques: (1) the physiological techniques of using implanted electrodes to stimulate and record from the brains of unanesthesized animals, and (2) psychological techniques for studying the behavior of these animals. These techniques have been combined in the study of escape and avoidance learning motivated by presumably noxious effects of central stimulation (Miller, 1953; Delgado, *et al.*, 1954), but the action of drugs on such centrally stimulated avoidance learning has not yet been studied. The slightly more recent and much more paradoxical effect, however—namely, that short periods of electrical stimulation of the brain can serve to reward a response such as bar pressing (Olds and Milner, 1954)—has been used to study drug effects. Olds *et al.* (1956) have shown that bar pressing reinforced by central stimulation in a variety of points in the brain is depressed by barbiturates, but that the action of reserpine and chlorpromazine seems to be more specific to electrodes located in the hypothalamus.

Need for Systematic Comparison of Different Measures of "Emotion"

In general, different investigators have each specialized in a single measure of "fear" or "emotional" response. We have used various forms of escape and avoidance learning (Mowrer and Miller, 1942; Miller, 1951) and have described some of these and a conflict technique in the present paper. Sidman (1953) has developed a somewhat different technique in which pressing a lever postpones the occurrence of electric shock. Brown *et al.* (1951) have used the potentiating effect of fear on the unconditioned startle response. Estes and Skinner (1941) have exploited the tendency of fear to produce "freezing" and to depress the rate of pressing a bar to secure water. Many investigators (whose work has been summarized by Lindsley, 1951) have used a variety of conditioned skeletal and autonomic responses.

There has been very little attempt, however, to determine the interrelationships among such measures by using a variety of them in experiments analogous to the very modest ones we have described for "hunger" and "thirst." For example, would the effects of a variety of drugs be similar on measures of

* We thank Mark A. Lund of the Squibb Institute for Medical Research, New Brunswick, N. J., for supplying the reserpine and also for some funds for this experiment by M. M. Berkun.

conditioned avoidance, conditioned suppression, autonomic responses, or approach-avoidance conflict behavior?

Concluding Remarks

Often there is agreement among quite different techniques for measuring the same effect. On the other hand, we have seen that under certain circumstances it is entirely possible for different techniques to yield opposite results, and even for the same technique to yield different results when applied under different conditions. Therefore we must be cautious in generalizing from the results of a single technique used under a single condition.

We must not be discouraged if our more sophisticated attempts to measure the same effect in a variety of ways yield confusing results. As we use standard, controlled conditions to determine the effects of a larger number of agents on a greater diversity of measures, designing our experiments so that exact cross-checks can be made, the pattern of interrelationships may take on a new and even simpler order. Who would have thought that one could find a single principle of gravity operating in such diverse phenomena as the falling of stones, in the floating of wood, the tides, and the motion of the planets? It is precisely because the concepts of physics, such as the law of gravity or the charge on the electron, can be checked by such a diversity of techniques, all of which agree beautifully, that we have such confidence in these concepts and that they have such power.

This paper has illustrated a number of rather diverse techniques for measuring motivational effects, but we have made only a modest beginning. Many other techniques can and should be devised and checked against each other.

As far as the screening of new drugs is concerned, the moral is obvious. Instead of depending on a single test, one should assemble a battery of diverse tests all aimed at supposedly similar effects. If one is in a great hurry and has reason to be confident in a single technique, one might use it as a coarse screen for the selection of promising drugs, but one should then subject these drugs to a more thorough analysis, using a variety of techniques. These subsequent tests will serve as a check on false positives, but false negatives will be completely missed.

We also need basic research in the development of a science of psychopharmacology. To take a specific example, the different results obtained in using reserpine and other tranquilizing drugs give me the uneasy feeling that some of the widely used screening tests may be measuring side effects that have a certain amount of face validity and a certain amount of specificity as regards reserpine but, nevertheless, are irrelevant to the psychologically useful effects of this class of drugs. We need analytical, basic research aimed at a better understanding of the clinically useful effects of these drugs. For that matter, we could benefit from a better understanding of drugs that have long been known to have beneficial psychological effects combined with undesirable side effects. If we had such understanding we should know how to devise superior techniques for screening other compounds and ultimately producing new and superior drugs.

Although the current interest in the tranquilizers has had the beneficial

effect of attracting a number of experimenters to the problem of investigating the psychological effects of drugs, I should hate to see the support of such work tied in too closely with the tranquilizing drugs. The history of psychiatry contains the skeletons of many wonder cures for schizophrenia. It is conceivable that the interest in the tranquilizing drugs will run a similar course. Even if these specific drugs should be disappointing, however, I feel certain that the general approach will prove fruitful. A combination of the vastly improved techniques of the chemist, the pharmacologist, and the experimental psychologist is certain to result in the finding of some drugs that will be of enormous clinical use—if not for curing schizophrenia, then for other purposes.

A science of psychopharmacology (or, if you will, behavioral pharmacology) can provide a rational basis for clinical and social application. Screening studies are valuable, but we need to develop also the basic science involved.

A number of years ago 6 life insurance companies collaborated in contributing a very modest amount, $1,500 per company each year, to a cooperative research organization. They formed the Life Insurance Agency Management Association, which sponsors industry-wide social-science research. More than 200 companies now participate in such research on a larger scale. This cooperative organization has produced results of the highest practical value in the day-by-day task of selling life insurance. I know that the pharmaceutical industry has a reputation for close competition. Nevertheless, in the long run, any fundamental scientific advance benefits the entire industry. Therefore I believe that, at this time, it would be highly statesmanlike and profitable for the pharmaceutical industry to form some sort of a cooperative organization to sponsor long range, fundamental research in the psychological aspects of pharmacology. Raymond Ewell (1955) estimates that in the United States, on the average, investments in research and development have repaid a dividend of from 100 to 200 per cent per year for 25 years.

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TECHNIQUE FOR STUDYING THE EFFECTS OF DRUGS ON DISCRIMINATION IN THE PIGEON

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I shall discuss a discrimination technique that is, as the saying goes, neither flesh nor fowl. In fact, this technique results from crossbreeding the flesh of the classical choice-box method with the fowl of the schedule-oriented operant technique. From the former comes the use of brief presentations of 2 response keys, 1 correct and 1 incorrect. From the latter come the recording of many responses—not just 1 per trial—on each of the keys and the use of a schedule of intermittent reinforcement to maintain this behavior.

Subjects

I have been using domestic pigeons as subjects, but no doubt rats or other animals would serve if appropriate changes in apparatus and reinforcement were made. Ferster[1] has noted some advantages of pigeons as subjects for research with operant methods and, earlier in this monograph, P. B. Dews has made a strong case for using pigeons in drug studies. My method uses food reinforcement, so that the pigeons are maintained at about 70 per cent of their free-feeding cage weight.

Apparatus

The basic pieces of apparatus are familiar from some of the previous articles in this monograph. They include an insulated, ventilated subject chamber containing response keys and a food magazine, and attendant relays, timers, and counters that constitute the automatic control and recording circuits.

My response-key and stimulus arrangement is shown in FIGURE 1. The pigeon confronts 2 recessed, semicircular translucent response keys separated by a vertical plastic partition. The visible edge of this partition forms a third stimulus element that I shall call the "bar." Either key may be lighted by the 6-watt lamp (left or right) behind it, and the vertical bar may be lighted by lamp *B*. The clear plastic partition conducts light from lamp *B* to the bar, but its sides are blackened to restrict the light from each lamp to its own stimulus area. The front view shows the response keys and bar as they appear to the pigeon. One of several possible stimulus patterns is represented. Only 1 key is lighted at a time, and the bar may be lighted or dark. Thus there are 4 possible stimulus arrays.

To make reinforcements as immediate and effective as possible, the grain-filled magazine is placed directly below the response keys. It can be raised within reach by a solonoid. During reinforcement an overhead lamp goes on and the grain rises within reach for about 2 seconds.

The present technique calls for a periodic tally of exact numbers of correct and incorrect responses. Cumulative recorders are not very well-suited to this

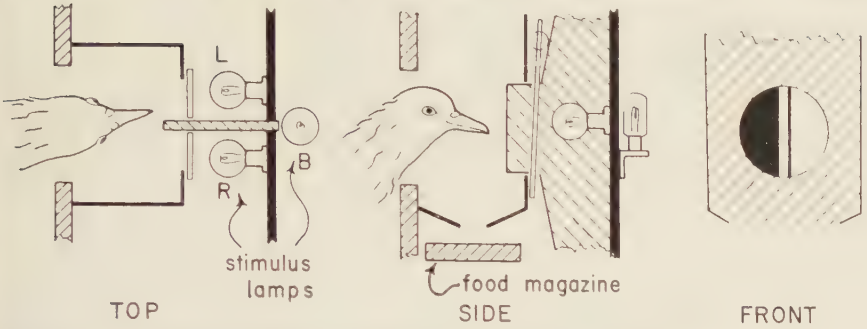

FIGURE 1. Stimulus and response-key arrangement. The "front" view shows one of 4 possible stimulus patterns.

job so, instead, banks of stepping switches "store" correct and incorrect responses. At intervals, the total number of responses in each category is "read out" onto a multipen polygraph. Marks on the record chart represent units, tens, and hundreds of responses, and these numbers may be quickly and directly transcribed.

Stimulus and Reinforcement Procedure

The discrimination that the pigeon makes is this: to get food it must peck the lighted key when the bar is dark, and the dark key when the bar is lighted. This is a "conditional" discrimination. That is to say, responding is not controlled by a single stimulus entity, but by 2 stimuli taken together—the key light and the bar light.

It is easy to reinforce pecks on the correctly lighted key, but it is somewhat more difficult to be sure that *only* the stimulus lights will be correlated with reinforcement and thus gain control of the pigeon's behavior. In a situation such as this, one often discovers that some unwanted behavior has been inadvertently reinforced. On the other hand, the behavior may be appropriate—too appropriate, in fact—and one finds that some unnoticed aspect of the situation has been tipping off the pigeon as to which key it should peck. Much of the experimental procedure consists of steps taken to prevent such spurious discriminations. I shall call attention to these steps as I go along.

The 4 stimulus arrays appear in a prearranged, balanced sequence designed to prevent spurious discrimination based on the order in which the arrays appear. Each array follows every other array an equal number of times. The sequence repeats after every 36 presentations, and I shall call these 36 presentations a "stimulus cycle." The events that occur during such a cycle are shown schematically in FIGURE 2. Each stimulus presentation lasts for 15 seconds (except when reinforcement occurs; I shall explain that in a moment) and each presentation is separated from the next by a 15-second "dark interval," during which all the stimulus lights are off (a "house light" in the subject chamber remains on at all times). There are 2 stimulus presentations per minute, so a full cycle of 36 presentations takes 18 minutes.

The figure shows that reinforcement does not occur during every stimulus

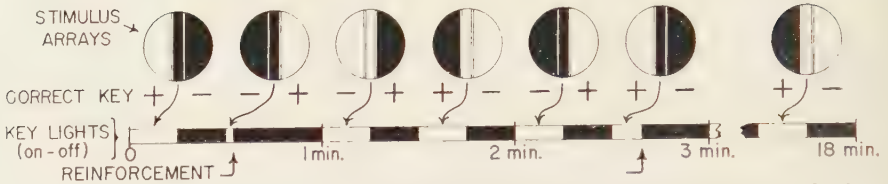

FIGURE 2. Diagram of events during one 18-minute stimulus cycle. A large portion of the cycle has been omitted.

presentation. In fact, correct pecking produces reinforcement only 12 times during every cycle. This spaced reinforcement, together with the brief 2-second eating period allowed, prevents satiation during a typical 5-hour experimental session. Correct responses to each of the 4 stimulus arrays are reinforced equally often. Pecks during the dark interval are never reinforced, and these soon cease.

Reinforcement itself could serve as an unwanted discriminative stimulus. If given the opportunity to peck after eating, the pigeon might simply disregard the stimulus lights and continue to peck the key that just paid off. To prevent this the keys go dark with each reinforcement and stay dark until the next presentation.

So that the pattern of reinforcement will not lead to a time discrimination - that is, different response rates in different parts of the presentation interval--a variable-interval schedule of reinforcement is followed. When reinforcement is scheduled to occur during a given presentation the apparatus reinforces the first correct response 1 second, 3 seconds, 6 seconds, or 13 seconds after the stimuli first appear. These intervals are assigned in equal numbers to each of the 4 stimulus arrays. If reinforcement is scheduled during a given presentation, however, and the bird makes no correct response from the time the reinforcement is due to occur until the end of the 15-second interval, the reinforcement is not carried over, but is lost to the bird.

Another possible spurious contingency must be dealt with. When 2 response keys are used, and the desired discrimination involves responding to only 1 of the keys at a time, there is danger that a so-called "superstitious" chaining of the 2 responses will occur. For example, it might frequently happen that the apparatus will ready a reinforcement just as the bird is pecking on the *incorrect* key. In that case the very first peck on the correct key that follows these incorrect responses would be reinforced. Instead of learning to make correct responses, the bird might learn to make one or more incorrect responses and *then* a correct response. It might even tend to obtain reinforcement by pecking the keys alternately instead of pecking only the correct key. To prevent these possibilities, incorrect responding is made to postpone reinforcement. Each incorrect response starts a 1-second timer and, during this 1 second, no response is ever reinforced. Since at least 1 second intervenes between each incorrect response and reinforcement, incorrect responding is relatively depressed, and alternation is discouraged.

Unwanted discriminations of a still different sort may arise from the fact that a reinforcement is lost if the pigeon fails to respond correctly to the stimulus

array after the reinforcement is scheduled to occur. Suppose the pigeon by chance missed several reinforcements in a row on 1 key. As a result, the rate of responding on that key would diminish, which might mean more missed reinforcements until the pigeon might end up pecking only the other key. The probability that this will occur is much reduced by a special pretraining procedure. Having first been trained to peck the 2 response keys at random (Ferster[1]), the pigeon gets 5 hours of pretraining. This training differs from the regular procedure in just one way: each presentation ends *only when the bird responds correctly and receives reinforcement*, and each stimulus pattern stays on indefinitely until ended by a reinforced correct response. This speeds up the acquisition of the discrimination and forces equal numbers of reinforcements for pecks on each of the keys. By the end of pretraining, the rate of pecking on the correct key is so high that few, if any, reinforcements are missed when the final procedure is instituted later on.

Base-Line Behavior

In studying drug effects I have used an experimental session lasting 5 hours and 24 minutes. This provides time for 18 stimulus cycles. At the end of each cycle total correct and incorrect responses are automatically recorded. The first cycle serves as a "warm-up" for the pigeon. After this the bird is removed from the box and given an oral dose of water or a drug solution. The bird is then replaced in the box.

I have found oral administration quite convenient. Using a syringe, it is

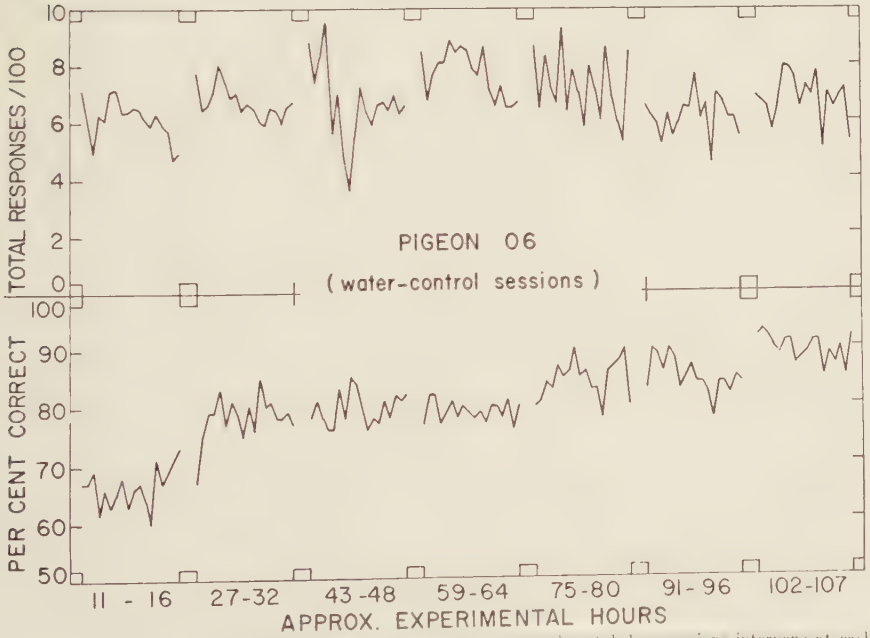

FIGURE 3. Part of the response history of 1 pigeon. Two experimental drug sessions intervene at each break in the curves. Each point represents responding during 1 stimulus cycle.

easy to avoid the pigeon's glottis and deliver a dose of up to at least 5 cc. directly to its crop.

In using this technique I have not trained the pigeons until a final, stable behavior base line has been reached. Stimulus control, as expressed in per cent of correct responses, increases slowly with the pigeon's experience, and drug effects are seen against this rising base line. A partial history of the responding of 1 pigeon is seen in FIGURE 3. The upper curve represents total-response output, and the lower represents the per cent of correct responses. The record begins after about 5 pretraining hours and after about 6 hours of the standard reinforcement procedure. Each segment of the curve comes from 1 session. Figure 3 shows only the records from water-control sessions of a drug study that I have reported previously. Two drug sessions intervene at each break in the curve shown here.

The somewhat erratic look of the curves may be partially forgiven if we recall that each point represents only about 8 minutes of actual pecking time. The over-all rate of responding remains at about the same level over the 100 hours of the experiment. The per cent of correct responses shows a gradual rise, averaging around 90 per cent during the last session.

An example of what can go wrong appears in FIGURE 4. These are data from the most deviant of 8 pigeons so far used extensively with this method. Here the pretraining was not permanently effective in preventing the formation of a spurious discrimination—in this case, a key preference. By the 48th hour the bird had simplified its task and was pecking almost exclusively on the right-hand key. The result was a decline in total response rate—the pigeon simply

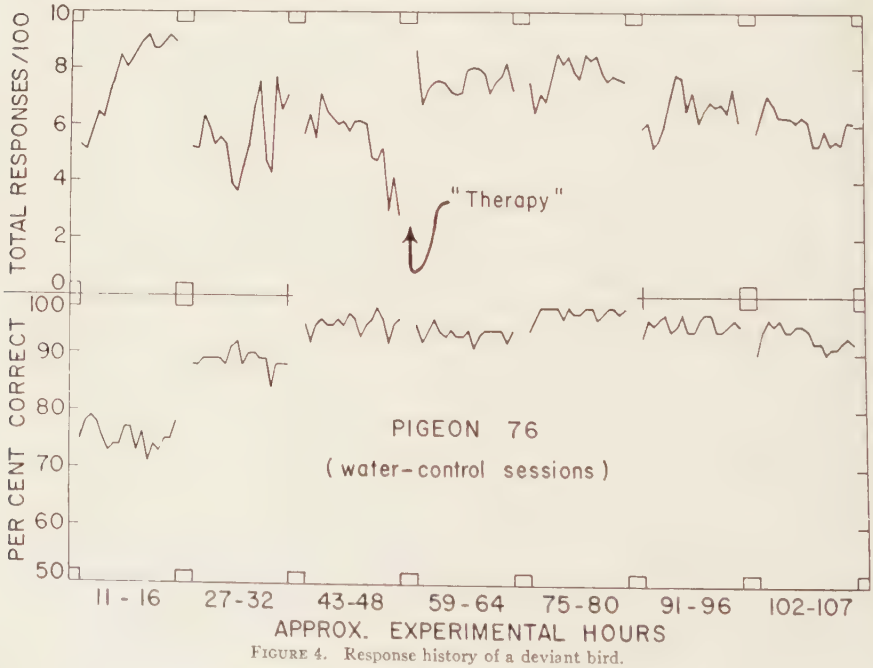

FIGURE 4. Response history of a deviant bird.

walked away from the keys when the left-hand key was correct—and a very high percentage of correct responses. At about the 58th hour a short session of "therapy" was given. During this "therapy" only the 2 stimulus arrays for which the left-hand key was correct appeared, and responses to the left-hand key were regularly reinforced. Subsequently, regular reinforcement followed correct responses to all stimulus arrays for a brief period. This therapy was only partially effective because, although the response rate climbed, responding to 1 of the 2 arrays for which the left-hand key was correct soon decreased once more. By the time the experiment was concluded, the bird was once again pecking the right-hand key almost exclusively. The per cent of correct responses remained very high, so it is not surprising that this is the only bird that did not show characteristic improvement in discrimination following administration of lysergic acid. It had no room in which to improve.

Illustrative Drug Effects

To illustrate what happens with drugs I shall refer to the results of a short study with 3 pigeons showing reactions to ethyl alcohol (1.6 gm./kg. in 25 per cent solution) and to sodium pentobarbital (10 mg./kg.). Each bird had 3 alcohol sessions and then 3 pentobarbital sessions. Water control runs alternated with the drug sessions. The birds had at least 2 days of rest after each session.

We see the effects of the drug and the subject variables in FIGURE 5. The connected circles represent mean alcohol data, and the unconnected circles are associated control means. Similarly, the connected dots are mean pentobarbital data, and the unconnected dots are controls. The zero points on the ordinate are the average of all the control points for each bird. All the data are given in terms of deviations from this mean control.

Both drugs initially reduce the per cent of correct responses, while total response output is increased beginning after about a half-hour. In general, pentobarbital has a greater effect on both measures than does alcohol at these dose levels. The effects decrease in a regular fashion with time and, at the end of 5 hours, they have almost disappeared. The effects of the 2 drugs have a similar time course.

The 3 pigeons responded in somewhat different ways. Pigeon 1 shows a relatively large reaction to pentobarbital, in terms of the per cent of correct responses. Pigeon 3 is resistant to effects on percentage change, but both drugs depress its initial total output. The response output of pigeon 2 exhibits very large increases under the influence of both drugs. This latter fact is especially interesting in view of the fact, not shown in the figure, that the control response rate for this bird was only about half as great as that of the other 2 birds. The control rate for pigeon 2 ran about 400 to 500 responses per cycle, and the others were between 800 and 1000 responses per cycle. These individual differences appeared consistently in the 3 individual sessions that make up each mean curve.

The time dimension of these results may supply a partial substitute for dose-response data but, at best, changes in time only suggest possible changes with dose. In a brief dose-response test, 1 pigeon was given single sessions

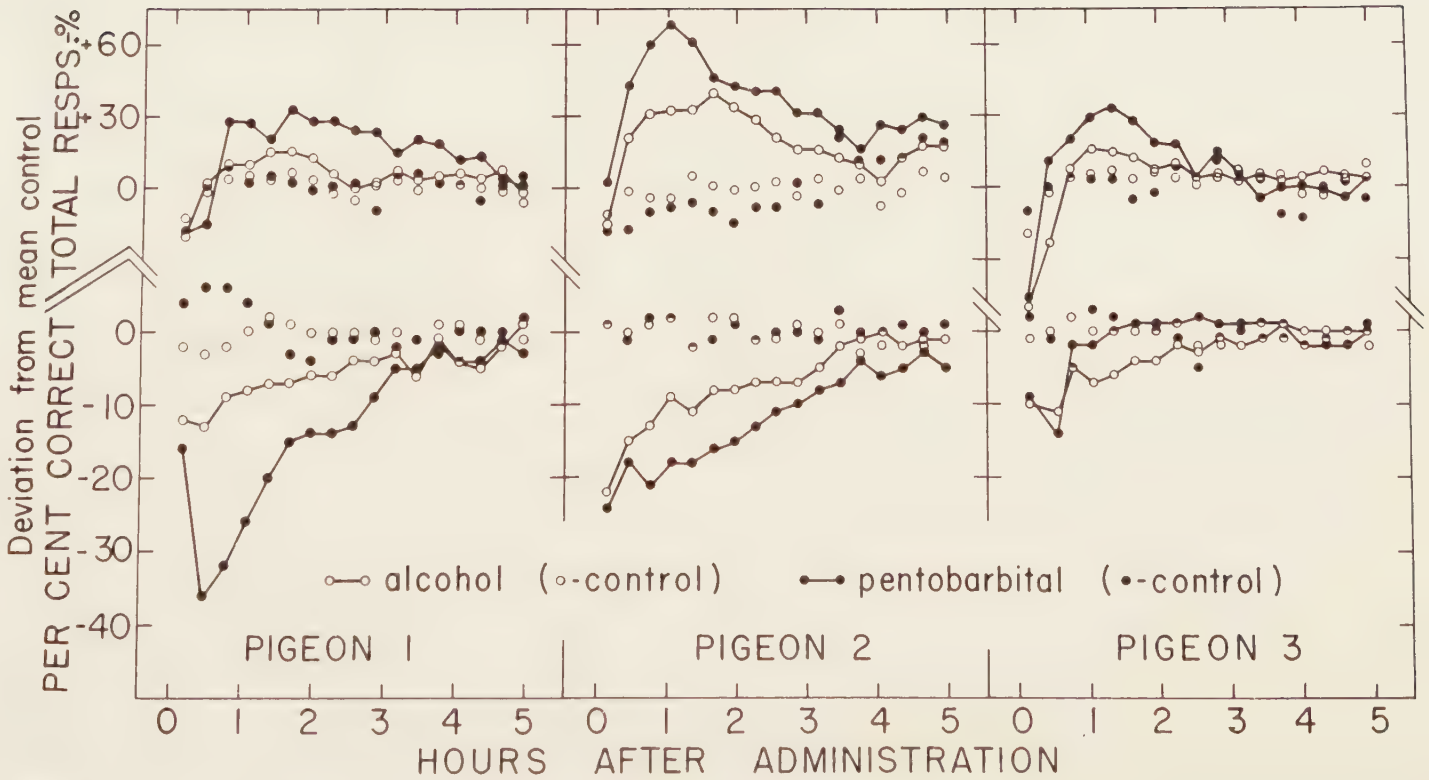

FIGURE 5. Effects of alcohol (1.6 gm./kg.) and pentobarbital (10 mg./kg.) with the time following oral administration. Each curve represents the mean of 3 sessions. Each point represents the responding during an 18-minute period (1 stimulus cycle). The unconnected circles and dots show data from water-control sessions.

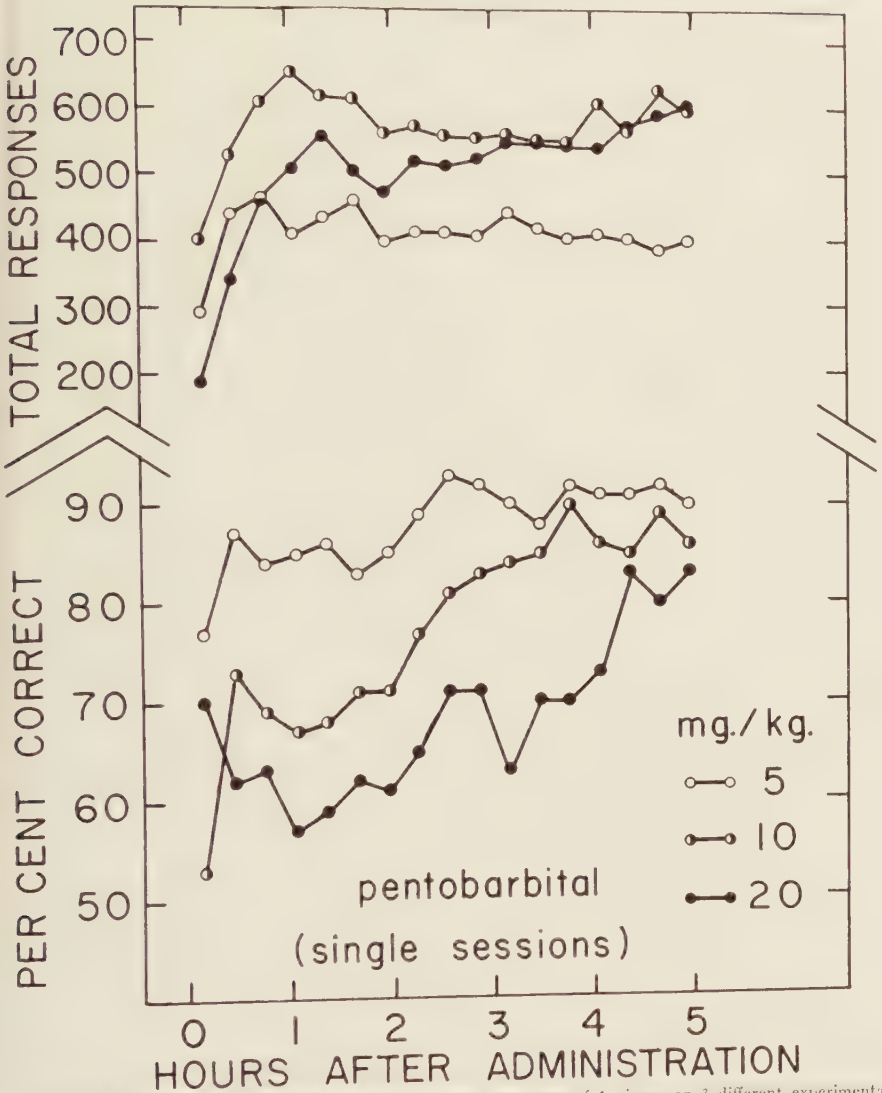

FIGURE 6. Total-response output and percent-correct responses of 1 pigeon on 3 different experimental days. A different dose of pentobarbital was given on each day.

with each of 3 doses of pentobarbital—5, 10, and 20 mg./kg. These results appear in FIGURE 6. Though these are only single sessions, the dose differences show up clearly in the per cent-correct curves and are in the expected direction. The greatest response rate occurred after the medium (10 mg./kg.) dose. This is not surprising in view of the fact that a very large dose would be expected to stop the bird's responding altogether (I have not attempted to determine the hypnotic oral dose for these pigeons).

Limitations of the Technique

One of the crucial features of the present method is its use of 2 response keys rather than 1. This feature raises several problems. We have seen in some of the previous papers that drug effects in even the simplest situations are hard enough to interpret. Each added complexity of stimulus and response multiplies the difficulties of analysis. In the present method, for example, how are we to specify the functional units of stimulus and response? Can we analyze the relative effects on the behavior of the different physical aspects of the stimulus—the bar and the key lights? Is the behavior of "switching keys" a response? If so, how do drugs affect this response? Does chaining of responses to the 2 keys occur, and do drugs disrupt such a chain if it forms? Detailed examination of response patterns in data from the present technique might suggest answers to some of these questions, but probably they can be clearly decided only by experiments specifically designed to answer them.

The gradual rise in the per cent of correct responses, as opposed to a stable control value for this measure, also adds to the difficulty of interpreting the results. First, of course, frequent control sessions are necessary in order to keep track of the base line. Second, it may be, as some unreported data suggest, that early in training some drugs have effects different from those which they later exert, when the per cent of correct responses has reached a high value. Third, when the base line approaches 100 per cent correct it becomes impossible to measure drug-induced improvement.

The most pressing difficulty with the method as it stands is the problem of reinforcements missed and resulting key preference or other unwanted discriminations. Extended pretraining could improve this situation. A solution might be to "store" the reinforcements missed when one of the stimulus arrays is on and to present them to the bird the next time the same array appears.

Advantages and Discussion of the Technique

The present method partakes of the many advantages of automatically controlled operant techniques and of pigeon subjects that were brought to our attention in earlier articles in this monograph. I need not repeat these, but I shall touch briefly on some of the more unique advantages of the present technique.

Several things suggest that the method might be helpful as 1 tool for screening and classifying drugs. It gives a rather fine-grain indication of drug effects through time. It seems to be sensitive to drug dosages that cause few or no grossly observable behavioral effects, although I have not studied such effects in detail. In so far as I have used the method, the effects measured have been reproducible and the effects appeared regularly in data from single sessions. In a single package the method provides 2 measures, response rate and per cent correct, each of which may vary up or down. This gives a relatively high probability that different drugs will produce different effects.

Of more theoretical interest is the possibility that a 2-response technique such as the present one may provide a more sensitive measure of discriminative behavior than a single-response method, because it may better isolate the

effects of the discriminative stimuli from the effects of other controlling variables. A crude example will illustrate this point. Suppose we set up 2 experimental boxes. In 1 box, correct and incorrect stimuli (S^d and S^Δ) appear alternately on a single response key; the bird pecks when the correct stimulus is on, but does not peck when the incorrect stimulus is on. In the other box, the 2 stimuli appear simultaneously on 2 keys, and the bird must choose the correct key. The percentage of total responses that are correct is tabulated for each box. Suppose that, in this situation, some event unrelated to the discrimination is introduced. This might be some subtle change with time, but gross changes make the best illustrations. For example, a drug might cause a period of vomiting, or someone might jostle the experimental boxes. If such changes occur in the single-key box during an S^d (correct stimulus) presentation, the pigeon slows down or stops responding and consequently the per cent of correct responses falls. If the pigeon stops responding in the two-key box, however, the situation is not prejudiced either way, and the per cent of correct responses remains unchanged. The point is that, in the single-key box, effects of variables that affect the over-all response rate are more likely to be confounded with controlling-stimulus variables.

Some of the data in FIGURE 3 may illustrate this point. In several places the response rate varied widely (we do not know why), yet the per cent of correct responses remained relatively unaffected. In the third session, for example (hours 43 to 48), the total-response rate varied over a range of more than 2 to 1, while the per cent of correct responses changed only 9 per cent.

We have seen that the gradual change in the per cent measure causes certain difficulties. I should like to argue against an overzealous search for a "stable base line," however. As with other behavior, "stable" behavior must be assumed to be under the control of various factors. Very stable behavior suggests a very powerful control by one or more such factors. Such control may override the effects of experimental variables—drugs, for example. To use a simple analogy: if in the study of water waves, a smooth, unruffled surface of water is desired as a base line, it does not do to freeze the water to achieve this base line.

This might be one way of looking at the insensitivity to drug effects of behavior maintained on a fixed-ratio schedule of reinforcement. If one observes behavior maintained by a ratio schedule, one is struck by the fact that it appears "driven." Powerful control appears to be operating. The behavior is "frozen," and a large amount of the experimental drug is necessary for the achievement of any effect.

Early in this paper I described as "conditional" the stimulus discrimination used in the present method. I used the term in a purely descriptive sense. It was not intended to imply that the pigeon was abstracting, or indulging in such reasoning as "*If* the bar is lighted, *then* I must peck the dark key." In a recent paper Dews[2] reported that behavior on a conditional discrimination was much more sensitive to the effects of drugs (pentobarbital and methamphetamine) than a "simple" discrimination in which 1 key color always meant "peck" and another always meant "don't peck." Dews pointed out that drugs generally are thought to exhibit their greatest effects on complex

behavior. What aspects of a situation make it "difficult" or "complex," and whether drugs may help us to discriminate between types of complexity, remain to be seen.

This line of thinking, together with clinical and common sense descriptions of the behavioral effects of drugs, suggest that we might profitably ask the following question: "How does a drug modify the action of each of the variables that control behavior?" The data I have presented are a few among many that indicate that drugs modify the control of discriminated stimuli over behavior. Further research might specify these effects more exactly. For example, does a drug appear to have effects only during S^{Δ}, or does it change S^{d} responding also? In another direction, does a drug differentially weaken newly acquired stimulus control and lead the animal to exhibit "old habits?"

It might prove interesting to compare the effects of drugs on stimulus control in a situation such as the present one with such effects in the conditioned emotional-response situation. In this latter situation we also find that drugs modify the degree of stimulus control of behavior. The stimulus is the warning signal; the behavior is both ongoing operant responding, which is suppressed, and "fear" responses, which are elicited by the stimulus. Some drugs appear to weaken this stimulus control, while others seem to strengthen it. These drugs are often thought to act by changing emotional responsiveness or, at any rate, by uniquely altering the effects of a history of punishment. This interpretation may well be correct. I am curious to know, however, if there is anything in common between drug effects on stimulus control in the conditioned emotional-response situation and drug effects on stimulus control in the operant-discrimination situation, of which the present method is 1 example.

Such considerations suggest a final question: "Can drugs help us to identify and analyze the variables that control behavior?" Judging from the facts and ideas presented in this monograph, I think perhaps the answer to this question is "Yes."

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THE DESCRIPTION AND ANALYSIS OF MOOD*

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There is some question in our minds as to whether the appearance at the end of this monograph of the only 1 of the 8 papers that deals exclusively with human subjects was planned as a climax or as an anticlimax. There is probably little question that the ultimate goal of research with drugs is to increase the understanding and control of human behavior and functioning. We have used human subjects, but good experimental work with complex human behavior — involving, as it does, incomplete control of the subject, his life history, and his environment—is difficult, tantalizing, and frustrating. We often wonder if there must always be an inverse relationship between the magnitude and importance of a problem in behavioral science and the adequacy of the scientific methodology by means of which it can be attacked. The rapidly growing list of publications on drugs and human behavior attests to the wide interest in and need for research in this area, but it leaves much to be desired from the point of view of methodology. Those of us who are rash enough to investigate these problems at the human level usually find that whenever we succeed in getting certain variables under reasonable control we merely highlight the importance of still other variables. Bridges from the work with animals to the work with human beings must be built, however. We shall discuss here some of the difficulties that we have encountered in the use of human subjects, and we shall suggest some ways in which these difficulties might be overcome.

In brief, we shall consider here: (1) a sample of the work on drugs done in the Department of Psychology at the University of Rochester; (2) the way in which our statistical analyses repeatedly reveal the operation not only of a variety of main effects due to specific factors, but also the almost overwhelming influence of these factors in complex interaction with each other; and (3) our use of an old but newly defined concept, the concept of mood, as the basis of a possible strategy by means of which research in drugs and research in other fields may fortify each other.

Since 1951, G. R. Wendt and the authors, together with a number of collaborators, have been involved in a series of studies of the effects of moderate dosages of commonly used drugs such as amphetamines, antihistamines, and barbiturates on the social, emotional, and motivational behavior of college men under varying degrees of experimental control and in normal daily routines (Harway *et al.*, 1953; H. H. Nowlis *et al.*, 1953; and V. Nowlis, 1953). The part of these studies with which the present authors have been primarily concerned has involved groups of 4 men interacting in a variety of situations in the labora-

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tory before and after the ingestion of moderate dosages of a drug or a placebo. Dosages used produced effects well within the range of normal variation experienced by the individual over a period of a month or a year. Over the 5-year period, 95 men have been observed in approximately 2400 hours of controlled social observation and in about 4800 hours of relatively free activity in the group-work aspects of our studies. Wendt and others have about 1800 subject-days in other than 4-man groups.

Each of the men for the group work was carefully screened by means of an interview and a battery of tests, both as a means for eliminating any subjects who might be harmed by participating and to give us a working knowledge of the personality of each individual. Only 2 potential subjects were eliminated: one because of a pattern of excessive drinking, and the other because of academic standing.

During any given year each of the men has gone through a procedure such as the following for from 4 to 18 times. Groups of 4 men, variously constituted, assembled in the laboratory for a standard lunch at noon. The relatively isolated laboratory is equipped with large, 1-way vision mirrors and high-fidelity sound recording. The subjects knew that they were being observed and recorded, but the microphones were inconspicuously placed and the mirrors so arranged that the men did not ordinarily see their own reflections; thus, for the most part, they reported and gave every evidence of forgetting about the mirrors and microphones. At this time the men filled out various forms designed to give as adequately as possible an assessment of their physical and psychological state.

During 2 years the subjects were given a variety of individual tests immediately preceding the group experiment. These tests included, on different occasions, perceptual, motor, and projective tests. They were repeated, after the administration of a drug, 3 hours later, at the end of the group session. During the actual group session the subjects were alone in the experimental room. On a desk beside their conference table was a pile of blue envelopes, each of which was labeled according to a time schedule. In the envelopes were instructions for each of their experimental tasks, various check lists, and blanks for partner ratings and group ratings. Also in the envelopes were the standard No. 2 white capsules that the subjects took orally at a designated time. Neither subject nor observer knew the contents of the capsules. The time to open each envelope was indicated by a buzzer controlled by an observer. Throughout the first and third hours of the session the subjects were alone. During the second hour they often took tests under the supervision of an assistant or studied under supervision in order to control the social interaction occurring during onset of the drug. During the first experimental (nonmedicated) hour the men performed from 3 to 5 tasks designed or chosen to highlight social participation, cooperation, competition, dominance, verbal output and reaction to frustration. These tasks included such activities as an adaptation of the French ball-and-spiral task, discussion of moral dilemmas or controversial current issues, role playing, assembling of lumber or of words, a 4-man electromaze, a vigorous and competetive "poke-board" task, and a rest period. During the rest period the men were free to do whatever they

wished within the confines of the experimental room, which contained such equipment as a dart board, books, and magazines. Interestingly enough, it was this free period that often provided the observers with the most useful cues on which they judged which medication was involved. The drug was taken during or at the end of this first hour at a time selected to have onset symptoms during the hour immediately following and to produce a steady state during the final experimental period, or third hour. During this third hour, tasks equivalent to those of the first hour were performed. By 4:00 P.M. the men were ready to rest, and by 5:00 P.M. they had decided at which downtown restaurant they would all dine. The process of arriving at this decision was an interesting one, and it varied predictably according to the medications the men had received. During the evening they returned to the laboratory for study or recreation, according to individual or group choice. Reaching this decision also provided interesting data. At 10:00 P.M. the men were escorted to their regular residences where they remained, under pledge to stay home and to do no drinking. They returned to the laboratory the following morning and filled out a further report.

Each year we have had more and more spontaneous volunteers, friends of current subjects, asking to be considered as subjects far in advance of the beginning of an experiment. Since we have used placebo and relatively unpleasant medications more frequently than drugs with desirable effects, we attribute our popularity to the fact that the men value the kind of contact that they have with each other and with the staff. It seems to some of them (the subjects include all types of men from art majors to engineers) an interesting way to learn about psychology. It should be added that we pay these volunteers at the rate of one dollar per hour for the period from noon to 10:00 P.M., and that we provide lunch and dinner.

While all this is going on, with the men producing their own data on the check lists and ratings of partners, the observers have made several kinds of records. The sound recorder has turned out a whole library of reels of tape, which we transcribed and tentatively analyzed only during the first year. We understand that this is not the only unanalyzed collection of tapes in the laboratories of the country! From time to time some observers have kept extensive impressionistic protocols. Some observers have recorded the Bales-Carter type of social interaction categories, and others have rated the men on scales roughly equivalent to the measures that we were obtaining from the adjective check list or predicting how each individual would fill out his short adjective check list at a given time.

The typical prodecure that we have just described represents a series of important decisions that we had to make in 1951 when we assumed the task of developing some methods for evaluating the effects of commonly used drugs on the socially relevant behavior of human subjects. Some of these decisions should be made explicit.

First, in the course of many years of research in problems of motion sickness, Wendt had found that it was feasible to administer certain drugs to college students under special laboratory conditions. Since we were in a college setting, we decided to continue work with college students in a college setting.

This decision has been justified, in one sense, by the fact that our 5-year record is free of accidents and serious repercussions. We feel that it is feasible and proper to do carefully supervised drug research with college men of appropriate age and character.

Second, we decided to have each man participate in a series of experimental sessions under a variety of drugs rather than just 1. Although this reduces the number of subjects observed, an important limitation because of extensive individual variability, it permits the observers to become acquainted with a man's typical social and emotional behavior in this group setting. Furthermore, the first time a college man takes a drug in a strange situation his behavior is perhaps less affected by the drug itself than by the uncertain and anxious expectations he has of what is about to happen. After several sessions the taking of standard capsules from which he experiences no earth-shaking effects becomes quite a routine matter for most subjects.

Third, we committed ourselves to the exploration of a broad spectrum of behavioral responses, including expressive behavior, self-perceived emotional responses, verbal reports of feelings and attitudes, coping behavior, defenses, and fantasy behavior.

Fourth, to avoid the intrusion of secondary responses to the stress of compelling physiological reactions, we have used only moderate dosages administered orally. By every self-report index available to us, the subjects were often not certain whether they had received a drug or a placebo.

Fifth, we worked "double-blind," as the current term puts it. Neither the subject nor the observer knew which of several drugs or lactose had been administered. Furthermore, we should suggest that under certain circumstances an even more rigorous control might be introduced, one that might be called "triple-blind," a situation defined as that in which the subject and the observer do not know what the drug is and, further, do not know what aspects of behavior may change with the drug. "Triple-blindness" is impossible to obtain in the professional patient-therapist relationship because the patient justifiably expects that what the doctor does is related to his symptoms and complaints. Current work by Wendt and Cameron at the University of Rochester on individuals with and without specific physical or psychological complaints suggests that concern with a major complaint may profoundly influence the effect of the drug.

Sixth, we set our subjects in social groups of 4 men, not primarily in order to study the effect of drugs on group dynamics, important as this would be, but to control and vary the social situation in order to reveal the socially relevant effects of the drug on individuals. Obviously this could not be done in an isolated individual. Moreover, drugs taken in everyday life act on individuals who are frequently involved in social situations.

Finally, the selection of drugs with which to work was made after 3 to 9 staff members had used the drugs themselves, in varying dosages, in both a standard social situation and during normal workdays. The existing literature was not very helpful in many instances. Furthermore, experience with the drugs led every staff member to realize that the few factors that can be specified, measured, controlled, and put into statistical analyses in drug research are

only a fraction of the operating variables. The kind of understanding that comes from such experience tends to protect one from unsagacious generalizations from inadequate data.

We shall now report a representative sample of our results. Although we have used routinely a variety of behavioral indices, we shall refer primarily to the 1 index in which, as research psychologists, we have become most interested; that is, the adjective check list for self-report of mood. You will wonder immediately and correctly, "How does self-report of mood correlate with other more objective indices?" It will be possible to answer this difficult question better after the completion of a series of studies now in progress on both medicated and nonmedicated subjects. In general, however, in the situations we have observed in the past, there is fair to good agreement among changes in self-report of mood and changes in such indices as ratings by partners, ratings by observers, and certain objective measures of performance such as verbal output in words per minute or number of tasks completed. In an emotional dimension such as elation-depression or hedonic tone, agreement is very difficult to achieve, but in a dimension such as task-involvement or hostile aggression, agreement is common. As a matter of fact, agreement among such indices raises just as many important conceptual and methodological problems as does disagreement (V. Nowlis, 1953).

Adjective check lists have been used in behavioral studies for at least 30 years. Harrison Gough, at the Institute for Personality Assessment Research of the University of California, Berkeley, Calif., has made the most extensive use of such an instrument, but his method differs from ours in procedure, content, and purpose. Whereas Gough is concerned with common agreement among judges who have studied a subject, we concentrate on self-report. Whereas Gough includes only adjectives that may describe the persistent qualities of the individual, the adjectives that we use describe moment-to-moment states of conscious mood (Gough, McKee, and Yandell, 1953).

Our check list consists of from 100 to 200 adjectives, the number varying with the purpose of the research and the kind of subjects used. We have also used the list in experiments where change in mood was brought about by means other than the use of drugs, such as deprivation of sleep, boredom, films, and mass communications with emotional content.

The subject is asked to read through the list rapidly and give his first response to each word. Four options to each word are permitted: a double check if the word definitely describes a strong feeling, a single check if it possibly describes a feeling, an "ignore" or "skip" if the word does not apply or if the subject is uncertain, and a straight-line crossout if the word definitely does not apply.

In checking behavior between predrug and postdrug conditions or between drug and placebo conditions, a very simple and useful method for the preliminary description of the effect of a drug in a specific situation is to examine in a group of subjects the words with the greatest change.

Dramamine usually produces a definite increase in the checking of such words as tired, drowsy, detached, sluggish, disinterested, dull, lazy, retiring, and withdrawn, and it produces a definite decrease in the checking of such words as businesslike, genial, industrious, talkative, cheerful, and energetic.

Partners' ratings and observers' ratings and protocols strongly tend to confirm such a picture.

Benzedrine typically increases the checking of such words as businesslike, talkative, capable, enterprising, independent and, sometimes, nervous and jittery, and it decreases such words as lazy, languid, and nonchalant. Benzedrine plus seconal, in small dosage, typically increases such words as generous, cheerful, industrious, expansive, expressive, talkative, and lighthearted. In higher dosages, the checking of assertive, confident, decisive, fearless, forceful, masterful, and uninhibited usually increases.

All this is not so simple. At first we used the same drug for all 4 men. In those sessions seconal, when compared with placebo, increased the checking of such words as expansive, forceful, courageous, daring, elated, and impulsive. In our first statistical analysis we were confronted with the stubborn fact that when the same drug is given to all 4 men in a group, the N that has to be entered into the analysis is 1, not 4. This increases the cost of an already expensive experiment by a considerable factor, but it cannot be denied that the effects of these drugs may be and often are quite contagious. Our first attempted solution was to run tests on groups in which each man had a different drug during the same session, such as 1 on seconal, 1 on benzedrine, 1 on dramamine, and 1 on placebo. What does seconal do? Cooped up with, say, the egotistical benzedrine partner, the withdrawn, indifferent dramamine partner, and the slightly bored lactose man, the seconal subject reports that he is distractible, dizzy, drifting, glum, defiant, languid, sluggish, discouraged, dull, gloomy, lazy, and slow! This is not the report of mood that we got when all 4 men were on seconal. It thus appears that the moods of the partners do definitely influence the effect of seconal. Furthermore, this influence, which is sometimes a relatively simple matter of contagion, may also involve much more indirect conflictive social processes.

Last year we faced this problem directly in one 4-week experiment. We selected 2 drugs that we understood fairly well, dramamine and seconal, and predicted that the former would be less influenced by mood of partner than would the latter. Haythorn (Haythorn, 1953) has worked out an ingenious schedule whereby, from a pool of 16 men, each man, over the course of 5 sessions, is never paired with the same partner more than once in 4 groups of men. We established 2 such pools of 16 men each. In one pool, each man had 1 session in which he was the only subject on dramamine while the 3 others were on seconal; he had 2 sessions in which he and 2 partners had dramamine, while the fourth had seconal; and in the fourth session he was on seconal as a stimulus partner for the other men on dramamine. This schedule permitted us to compare the dramamine effect when the subject was grouped with 3 partners on seconal with the dramamine effect when he was in a group predominantly on dramamine. For the other pool we developed a similar schedule to compare the effect of seconal in the presence of partners who were predominantly on the same or different drug.

Three main instruments were used: (1) a long adjective check list administered at the start and finish of the 3-hour session; (2) a short adjective check

list for self-report after each of the 3 tasks in the predrug and postdrug periods; (3) the same short adjective check list filled out independently by 2 observers who had been taking protocols with the definite aim of discovering those specific behavioral changes that seemed crucial to them, after thousands of hours of experience, in the discrimination of medicated from nonmedicated behavior. Each observer filled out a check list for each subject as he predicted that the subject would fill it out at the same time.

In scoring the long adjective check list, we used 18 clusters of adjectives that we had derived empirically from the check lists of 100 men in a classroom situation. The short adjective check list consisted of an almost synonymous pair of words from each cluster and 7 other pairs of words representing aspects of mood that we felt had not emerged from the lecture situation. Until we know all there is to know about mood, users of the adjective check list should not hesitate to add words selected for specific purposes.

The analysis of the data involved 136 different analyses of variance. First, to put the observers' over-all records in perspective, we found that they correctly predicted the direction of change of mood in 18 of the 25 clusters under dramamine and in 23 of the 25 clusters under seconal. The statistical analyses indicate that each observer did far better with some subjects than with others, and better on some clusters than on others. Moreover, the 2 observers differed as to which subjects or clusters let them perform with maximum skill and insight.

As indicated both by observers and by self-report on the adjective check list, dramamine in the over-all analysis produced its usual effect of decreasing the score in the clusters of active words and increasing scores in the clusters of sleepy and inactive words. There was not the usual decrease in scores of the clusters with words denoting positive social orientation. Seconal produced its usual effect of increasing control and words of elation such as vigorous, mischievous, original, willful, and cheerful, but, somewhat as dramamine did, seconal slightly decreased scores in the active and industrious clusters.

The main hypothesis, namely, that a subject on seconal is more influenced by the mood of his partners than is a subject on dramamine, received strong support. The contribution of the group $\times$ drug (G$\times$D) interaction term to the total variance is our test of whether or not the effect of the drug differed according to the kind of drug the subject's partners had received. G$\times$D interaction was significantly large in 2 of the 25 clusters under dramamine and in 8 of the 25 clusters under seconal. To put it in another way, the G$\times$D interaction term was significantly large in 5 per cent of the 68 analyses of dramamine and in 19 per cent of the 68 analyses of variance involving seconal.

A subject on dramamine in a predominantly seconal group checked less frequently words in the "disturbed and jittery" clusters than when he was in a group that was predominantly on dramamine.

The G$\times$D interactions in the seconal analysis reveal a very interesting effect. When the lone man on seconal is grouped with 3 men on dramamine, he reports that he is more industrious, careful, vigorous, boastful, jittery, and defiant, and that he is less drowsy, leisurely, and intoxicated than when he has

2 other partners on seconal. Three sluggish dramamine partners seem to sober him, alert him, and annoy and frustrate him. He reports a more positive mood when others are also on seconal.

Significant main effects due to task differences and to individual differences among the subjects were found in 11 per cent and in 45 per cent of the analyses, respectively. These factors significantly interacted with drug effects in 13 per cent and 42 per cent of the analyses, respectively. That the nature of the task influences the effect of the drug is not surprising, and it suggests the general importance of evaluating results in terms of the specific task used in any experiment on drugs. Everyone expects, of course, to find individual differences in drug effects. Since we have not had more than 32 men in any single experiment, our samples have been too small for us to make a satisfactory search for the personality variables related to drug effects. We have nevertheless examined scores from many personality tests in an attempt to understand these individual differences. No standard personality test has yet helped us to predict with any degree of certainty individual differences in either the effect of a drug or social behavior in group situations. This is just another example of the general finding in social psychology that prediction of behavior in experimental social groups is not yet possible on the basis of any of the well-known personality tests (Festinger, 1955).

The many statistical analyses that we have run, supplemented by our best judgment of factors that do not get into the analyses, suggest that the effects of behavior-modifying drugs in moderate dosage are influenced by differences among specific individuals, specific situations, and specific tasks. These factors not only differ in many ways, but they also interact with each other. It would seem that progress in research on drugs is going to remain dependent on progress toward the solution of the main problems of psychology.

The adjective check list has become one of our most important instruments, and mood is now one of our most useful concepts. Both have evolved slowly over the 5 years of research in drugs. It is difficult to develop an instrument with which to determine the validity and reliability of work on the numbers of subjects that we feel we can handle, and pay, in such research. We now feel that we should deal with the description and analysis of mood as a problem in its own right. In doing this we hope to develop the adjective check list to a point where it is not only a better method for studying the effects of drugs, but one that is applicable to a wide variety of situations not involving drugs.

In a paper on Current Trends in Psychology, read in 1956 at the University of Pittsburgh, V. Nowlis (1956) suggested that mood may be defined as an intervening variable or predispositional factor that is a source of information, or discriminable stimuli to the organism, about the current functioning characteristics of the organism. Conscious mood consists of the perceptual and cognitive responses to this information.

Mood as an intervening variable may have a direct (unconscious) effect on the probabilities of occurrence of certain responses in certain situations, as in expressive behavior and action. Here mood is like Skinner's (Skinner, 1953) concept of predisposition, a state that directly changes the probabilities of certain acts in certain situations. Mood, as an intervening variable, however,

may have other relations that might be ignored if only the direct change in probabilities of certain acts is considered.

We assume that mood has a cue function when we define conscious mood as the response to discriminative stimuli supplied by the hypothetical mood state. We may also make the assumption, perhaps gratuitously at present, that these cues, which supply information about the current functioning of the organism, are involved in the self-monitoring and self-regulation of complex behavior.

Human organisms learn to label or to respond verbally to their conscious mood, and to discriminative stimuli supplied by mood as an intervening variable, with thousands of adjectives and descriptive phrases. The availability of these verbal responses gives us our best present index of changes in mood following experimental operations.

Our previous work has shown that verbal report of mood changes not only with certain experimental operations, but is also under the influence of a good many extraneous factors such as individual differences in readiness to check socially acceptable or unacceptable words, the position of the word in relation to other words in the list, and the dominant set to check, to ignore, or to cross out words. We hope to develop ways of minimizing the effects of these factors as we go along.

It is quite possible that mood may also influence behavior indirectly by way of these verbal or mediating responses. An individual who becomes tired in an unusual place at an unusual time will probably arrive at a resting place more quickly as a result of self-report of fatigue.

Mood is usually regarded as a more or less persistent state. A useful but arbitrary discrimination between the concept of emotion and that of mood is that the duration of emotion is shorter than that of mood. When both factors are involved in the same behavior sequence, we suggest that emotion is the onset and mood is the subsequent steady state. The initial emotional response may be more intense and may be associated with explosive action very difficult to observe objectively or subjectively. By contrast, mood may be relatively less intense, but more available for inspection and report. By shifting our research focus from emotion to mood we concentrate on the steady state that can be observed with some reliability and ignore, for the present, the rapid, complex, and important onset.

We can now try to anchor this intervening variable down to some antecedent experimental operations. There seem to be at least 3 classes of such determinants: (1) operations such as deprivation, threat, pain, frustration, restraint, conflict, sexual stimulation, success, and reward that elicit emotional responses and thus indirectly influence mood; (2) operations that bring about persistent intraorganic processes and events such as metabolic and physiological changes, illness, shock, postoperative states, fatigue, and brain injury (drugs would be included in this class); and (3) persistent environmental stimulation or deprivation.

As stated above, we are engaged in a series of studies with nonmedicated subjects in which some of the behavioral consequents of changes in mood are being investigated. A most promising lead comes from the work by Janis and

Feshback (Janis and Feshback, 1953) at Yale University, New Haven, Conn., and Haefner (Haefner, 1956) at the University of Rochester, indicating that the level and the type of report of changes in mood are associated with the degree of acceptance of a recommendation in a persuasive communication. The latter study and the studies in medication yield abundant evidence that the words in the adjective check list change in significant ways with experimental operations. Moreover, the words change together in ways that produce interesting clusters, but these empirical clusters are not satisfactory because they are not sufficiently trans-situational, and they are not useful in the search for general laws. For example, the 18 empirical clusters based on the responses of 100 men in a classroom situation that were used in the analyses just discussed did not have maximum sensitivity to changes brought about by drugs, while other clusters derived from data on drugs reflected with maximum sensitivity certain effects of drugs, but were not generally applicable even to different drugs, or to the same drug in different circumstances. How can generally applicable categories be discovered? Recently McClelland (McClelland, 1955) suggested that "we are inextricably involved in the analysis of some of the myriad verbal responses which describe mental content: and in such an analysis we must find categories which are meaningful; they must be related to theory; they must be trans-situational —*i.e.*, they must be applicable to more situations than the one to which they are first applied. It takes inspiration or luck or hard work or something to discover such a category; the only concrete suggestion I have . . . is to choose those categories which show significant shifts as a result of experimental operations."

In the search for meaningful categories we are just completing a 6-week experiment in which 400 college men without medication reported their moods each week before and after motion-picture films selected to produce intense mood change. With the help of the IBM 650 digital computer, obtained from the International Business Machines Corporation, New York, N. Y., soon to be installed at the University of Rochester, we shall do factor analyses on 1 of the pre-experimental check lists and on each of the 6 postexperimental lists. Factors that emerge in all 7 of these analyses should be relatively trans-situational. Analysis of pre-experimental and postexperimental differences will indicate how factor scores change with experimental operations.

To guide us in developing the broadest possible base for the list of adjectives used in this current experiment we have postulated 4 bipolar dimensions of mood, each of which reflects our initial assumption that mood as an intervening variable supplies information about the current functioning characteristics of the organism.

The first postulated dimension is *level of activation*, which refers to that aspect of mood in which there is perception of readiness for such actions as moving, acting, responding, working, thinking, and paying attention; and in the negative pole, there is perception of readiness to rest, sleep, and remain inactive. Both Lindsley (Lindsley, 1951) and Schlosberg (Schlosberg, 1954) have discussed a concept of activation in the study of emotion. Osgood (Osgood and G. Suci, 1955) has found this concept to be 1 of the main factors in the connotative meaning of words.

Second, *level of control* refers to that aspect of mood in which there is perception of the degree to which internal and external events are, have been, or will be under control, or the degree to which they are out of control. This is slightly similar to the traditional organized-disorganized dichotomy.

Third, *social orientation* refers to that aspect of mood in which there is readiness for interaction with other persons or readiness to hurt, reject, or ignore others.

Finally, *hedonic tone* refers to that aspect of mood in which there is perception of pleasantness or unpleasantness. It is the classic dimension in the description of mood and feeling.

Before the end of 1957 we shall know how well our postulated dimensions agree with those that come out of the factor analyses. Thereafter, given an instrument with some generality, we can search more efficiently for relations between antecedents and consequences and between the report of a change in mood and other associated changes in behavior. We feel that these present interests are an example of the way in which the interesting problems encountered in research in drugs may stimulate new work in a general science of behavior.

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